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MANUSCRIPTS: All manuscripts should be addressed to the Editorial Office of the Journal, 49 West 45th St., New York 36, N. Y. *Style for bibliography:* DOE, J. J. Treatment of hypertension. Am. J. Med., 6: 72, 1948.

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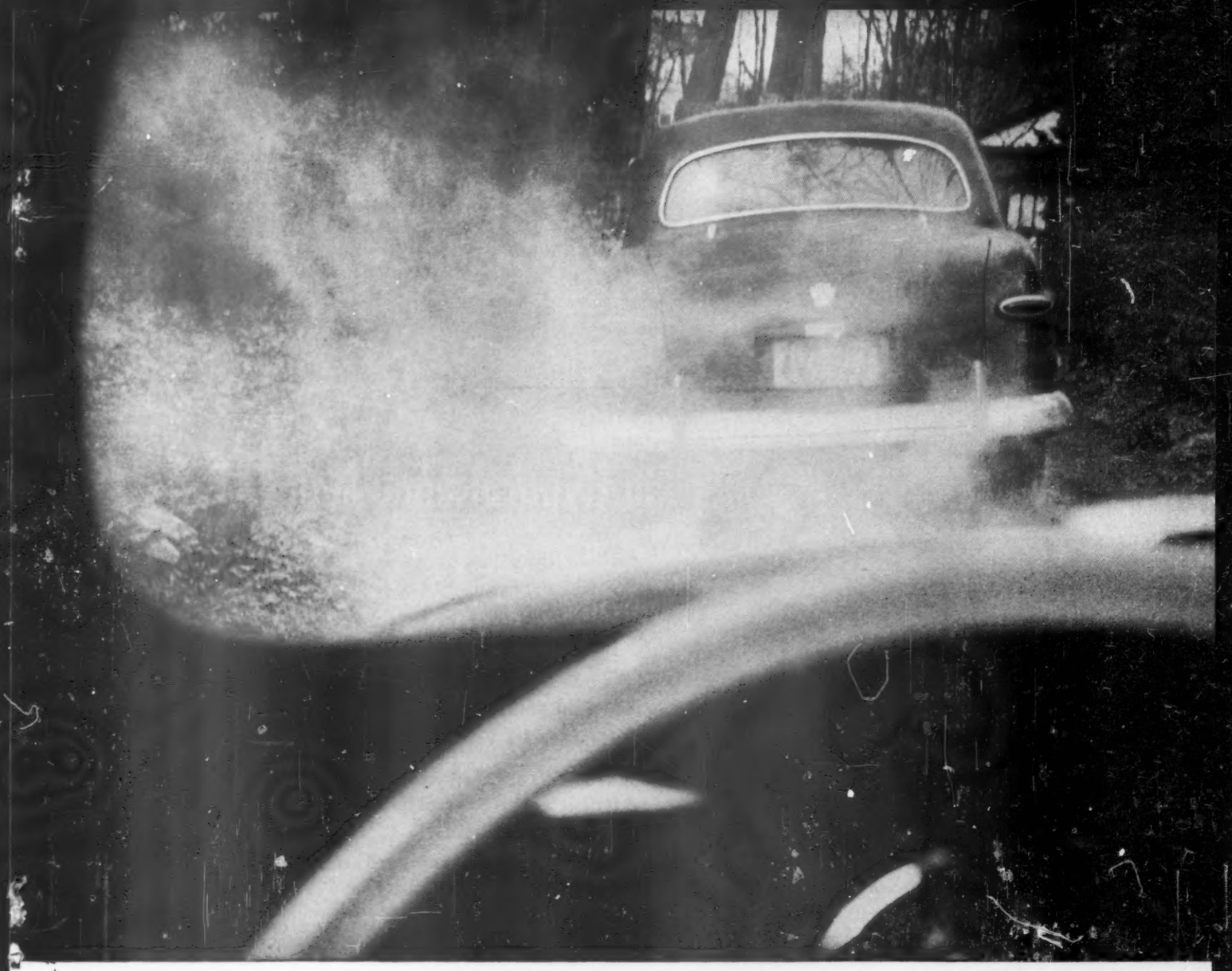

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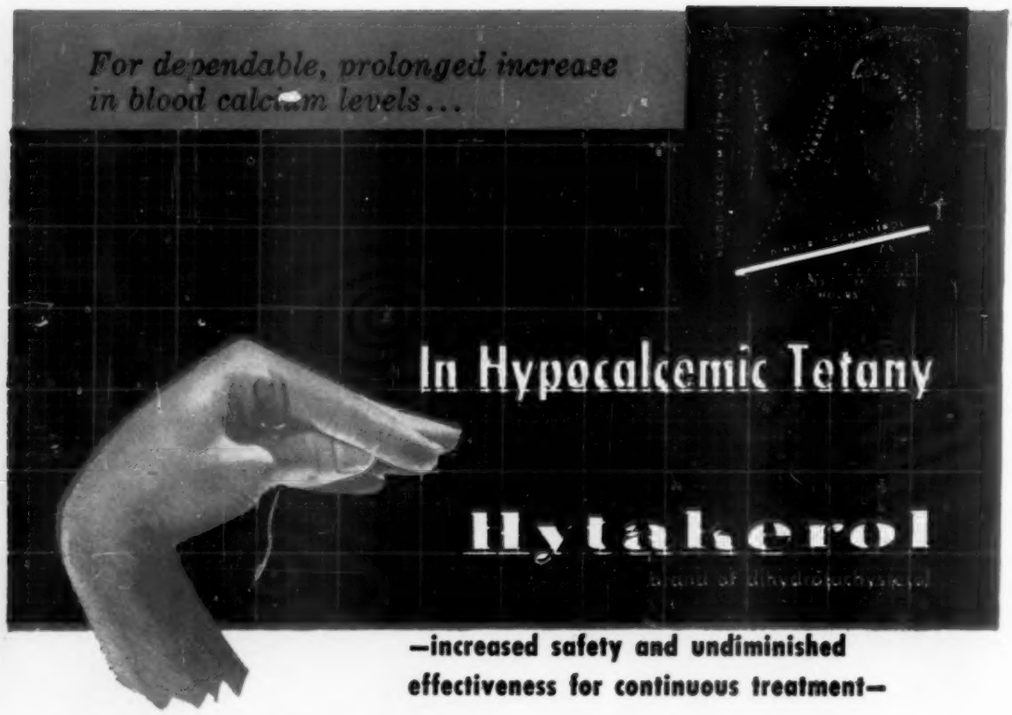

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1. Grollman, Arthur: Essentials of Endocrinology. Philadelphia, J.B. Lippincott Co., 2nd ed., 1947, p. 269.
2. Sandock, Isadore: Tetany and ovarian function. *J.A.M.A.*, 160:659, Feb. 25, 1956.

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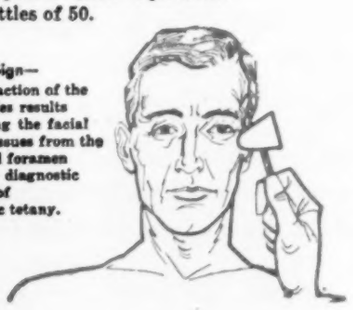

Chvostek's Sign— Tonic contraction of the facial muscles results from tapping the facial nerve as it issues from the stylomastoid foramen —one of the diagnostic indications of hypocalcemic tetany.

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Clinical Studies

Further Observations on Patients with Malignant Carcinoid
ALBERT SJOERDSMA, HERBERT WEISSBACH, LUTHER L. TERRY AND SIDNEY UDENFRIEND 5

The "classic" concepts of carcinoidosis are rapidly expanding as more cases are studied and the diagnosis is established earlier by detection of urinary excretion of 5-hydroxyindole acetic acid. This is brought out instructively in the present analysis of nineteen cases. Of special interest is the estimate, by use of labeled 5-hydroxytryptophan, of the enormous tumor pool of serotonin and of its turnover rate in a case of metastatic carcinoid; also, the evidence of tryptophan depletion because of the inordinate demands of the tumor tissue for biosynthesis of serotonin. The implications of these findings throw additional light on the role of serotonin.

Determination of 5-Hydroxytryptamine, 5-Hydroxyindole Acetic Acid and Histamine in Thirty-three Cases of Carcinoid Tumor (Argentaffinoma)
BENGT PERNOW AND JAN WALDENSTRÖM 16

The authors have had opportunity to study thirty-three patients with carcinoid tumors and report on the results of the determination of 5-hydroxytryptamine in serum and of a metabolite, 5-hydroxyindole acetic acid, in urine. The value of these determinations in the diagnosis of carcinoidosis has now been well established. It is shown that complete resection of the tumor results in return to normal of these values, another indication of their physiologic significance and a means of establishing recurrence of tumor. Other interesting correlations are brought out, a particularly intriguing one having to do with concomitant increase in the urinary excretion of histamine.

Lactescence of Serum Following Episodes of Acute Alcoholism and Its Probable Relationship to Acute Pancreatitis . MARGARET J. ALBRINK AND GERALD KLATSKIN 26

It has long been known that acute alcoholism may be followed by acute pancreatitis. The present report calls attention to an interesting manifestation of the acute pancreatitis occurring under these circumstances, namely, transient lactescence of the serum due to hyperlipemia. This phenomenon is one aspect of the complex relationship between pancreatitis and hyperlipemia, which is discussed informatively in some detail.

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The Pattern of Intermediary Carbohydrate Metabolism in Cushing's Syndrome
DOROTHY H. HENNEMAN AND JOHN P. BUNKER 34

It is shown that under various conditions of glucose loading there is excessive accumulation of lactate and pyruvate in the venous blood of patients with Cushing's syndrome and of subjects receiving 17-hydroxycorticosteroid therapy. The abnormal responses described appear to be peculiar to the states indicated. The inference is drawn (although all the facts are not adequately explained) that the 17-hydroxycorticosteroids inhibit the conversion of pyruvate to acetyl coenzyme A and carbon dioxide, without affecting the tricarboxylic acid cycle directly.

Fructose and Diabetes . . . . . JOHN A. MOORHOUSE AND ROBERT M. KARK 46

This paper is timely in view of current interest in fructose as a medium for management in diabetic ketosis and the light thrown by its use upon the nature of the metabolic defects in diabetes and the actions of insulin. Fructose was delivered to the diabetic patients under experiment by continuous tube feeding, insulin having courageously been withdrawn. In the patients with milder diabetes there was improved utilization of carbohydrate, and with this, improved utilization of fat and protein. In the patients with severe diabetes fructose administration was ineffective. Apart from the impracticality of continuous oral feeding, a prerequisite for reasons made clear in the text, the authors conclude that fructose has little therapeutic usefulness. They go on to make deductions as to the site and nature of the metabolic block in diabetes, and on the action of insulin.

The Management of Hepatic Coma in Relation to Protein Withdrawal and Certain Specific Measures
W. H. J. SUMMERSKILL, STANLEY J. WOLFE AND CHARLES S. DAVIDSON 59

The authors review their large experience in the management of hepatic coma, for the most part in patients with advanced alcoholic cirrhosis. The regimen which yielded more recoveries than any other employed included protein withdrawal from the diet, oral administration of broad-spectrum antibiotics and judicious use of enemas; supplementary use of glutamic acid, aspartic acid, lipoic acid or corticosteroids did not improve the response significantly. Concurrent blood studies, notably of ammonia, were made. The authors make clear that the problems of pathogenesis and treatment of hepatic coma have not been resolved by any means.

The "Dieting Depression." Incidence and Clinical Characteristics of Untoward Responses to Weight Reduction Regimens . . . . . ALBERT J. STUNKARD 77

In this important study, Dr. Stunkard stresses the generally overlooked or but dimly perceived point that about half of all obese persons who undertake more or less strenuous weight reduction regimens experience untoward symptoms. He describes one such untoward response, the "dieting depression," which is all the more likely to be unanticipated because it is preceded by a period of undue enthusiasm or elation. It is made clear that, far from being the innocuous procedures generally supposed, weight reduction regimens impose some hazard, particularly in subjects who have previously exhibited instability—and since obesity may itself be a manifestation of poor life adjustments, the hazard is not confined to few.

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now *". . . care of the man rather than merely his stomach."*

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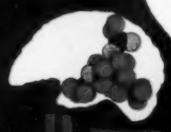

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Cardiac Involvement in Coccidioidomycosis . MYRON G. CHAPMAN AND LEO KAPLAN 87

A report, well documented with clinical and pathologic data, of proved coccidioidomycosis of the heart, chiefly involving the pericardium. Apart from its intrinsic interest, this report will serve as a reminder of the ubiquitous spread of the disease in its disseminated form and of the fact that the infective areas of coccidioidomycosis are no longer restricted to the two celebrated valleys.

Hydatid Disease in Alaska . . . . . .THOMAS R. A. DAVIS 99

An interesting ecologic and epidemiologic study of echinococcosis in Alaska, with implications of considerable interest for other infected areas.

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Temporal Lobe Epilepsy: Brief Review. Responses on Electrical Stimulation of the Amygdaloid Region in Six Patients
WILLIAM P. CHAPMAN, MADAN M. SINGH, HEINZ R. SCHROEDER AND CHARLES FAGER 107

The subject of temporal lobe epilepsy, herein reviewed and illustrated by six case reports, should be more familiar to the physician because it is a not uncommon form of epilepsy, is usually resistant to anticonvulsive medication, and is frequently associated with personality disorders. The present study is of interest particularly because electrical stimulation of the amygdala in the six cases described quite faithfully reproduced the manifestations of temporal epilepsy, even to oddities of aura and behavior in individual instances. Coagulation of the amygdaloid region by means of implanted electrodes is proposed in treatment.

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Current Concepts of Lipide Metabolism . . . . . D. B. ZILVERSMIT 120

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Conference on Therapy

Drug Reactions 134

Conference on Therapy (Cornell University Medical College)—This conference is required reading. It deals with those elementary facts of variation in biologic response which are so often lost

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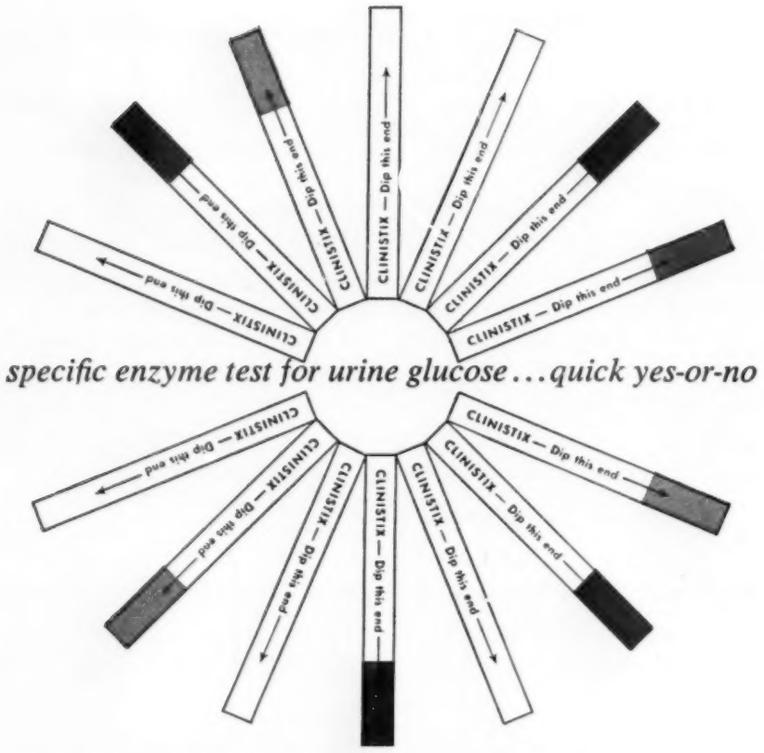

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sight of in the administration of therapeutic or diagnostic agents, sometimes with disastrous results. The dangers multiply as the number and potency of the agents employed increases, a pertinent point in this age of renascent polypharmacy.

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Dysproportionate Dyspnea in Recurrent Cardiac Insufficiency 142

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Skin-covered Mediastinal Teratoma Simulating a Fetal Parasite. A Review of Mediastinal Teratogenesis

J. WINTHROP PEABODY, JR., LAWRENCE H. STRUG AND HOWARD A. BUECHNER 153

The case described, of a benign skin-covered mediastinal teratoma successfully removed, is of unusual interest and is followed by an engrossing account of teratoid tumors, which make up a significant proportion of tumors of the anterior mediastinum. The authors hold that, all benign teratomas being potentially malignant, surgical excision is always indicated, and without undue delay.

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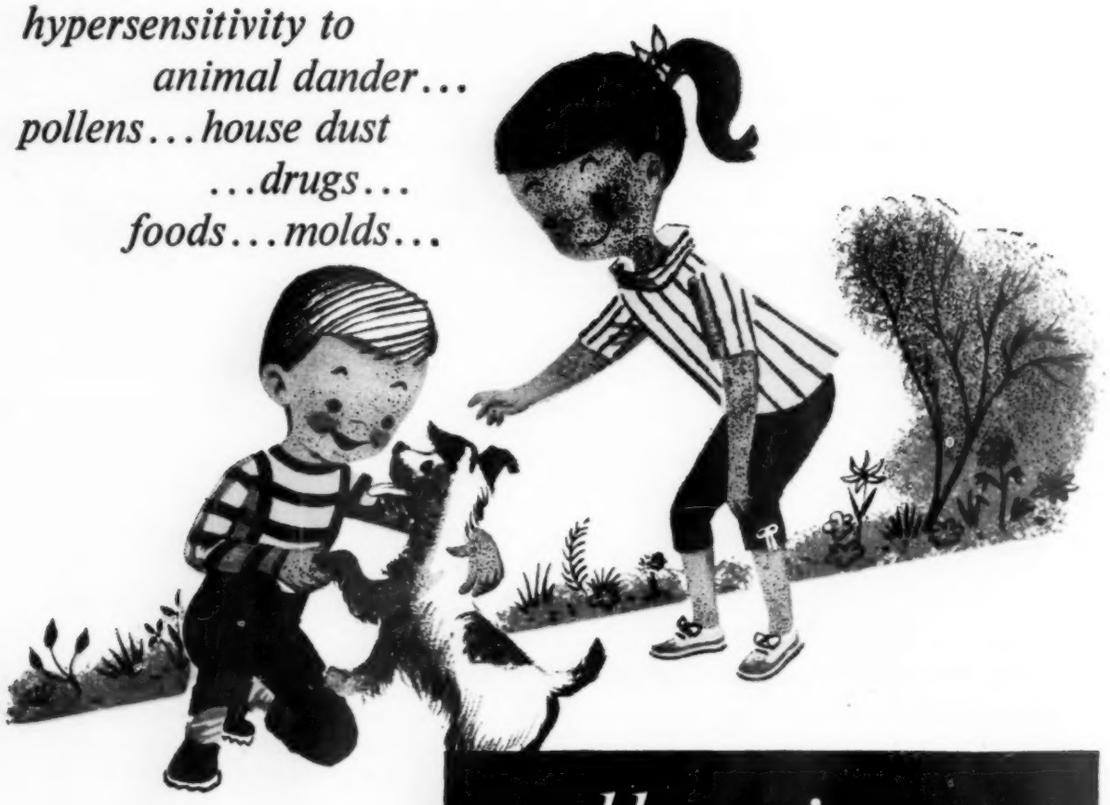

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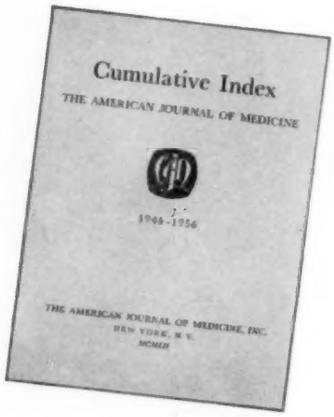

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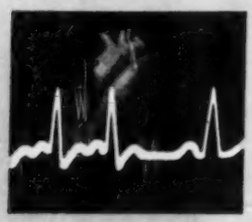

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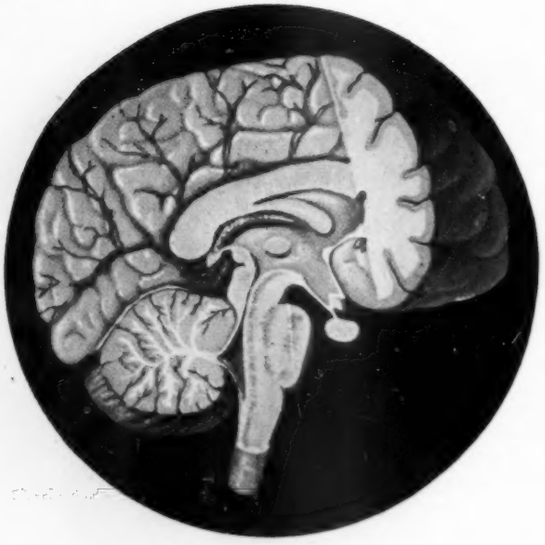

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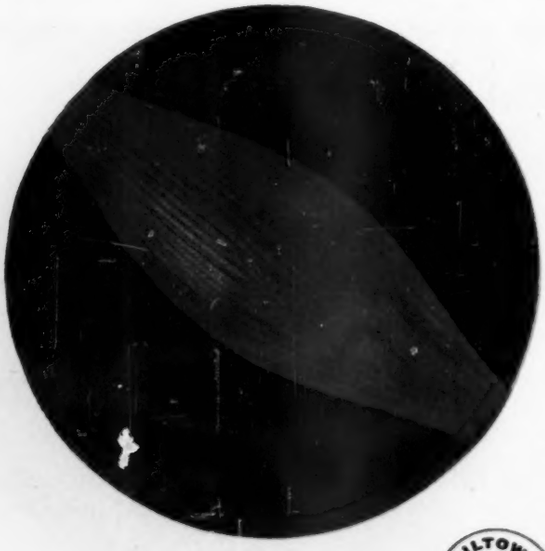

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tranquilizer with muscle-relaxant action

2-methyl-2-n-propyl-1,3-propanediol dicarbamate—U. S. Patent 2,724,720

Supplied: 400 mg. scored tablets
200 mg. sugar-coated tablets

Usual dosage: One or two 400 mg. tablets t.i.d.

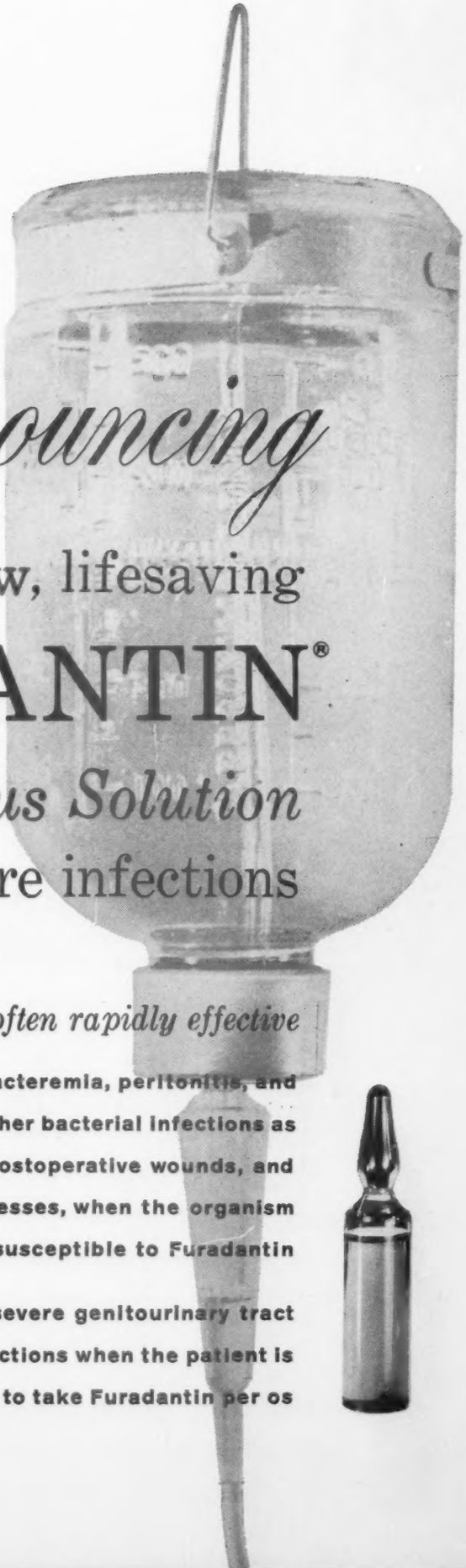
Literature and samples available on request

MILTOWN® THE ORIGINAL MEPROBAMATE

DISCOVERED AND INTRODUCED BY WALLACE LABORATORIES

WALLACE LABORATORIES
New Brunswick, N. J.

CM-8109



Announcing

new, lifesaving

FURADANTIN®

brand of nitrofurantoin

Intravenous Solution

for severe infections

often rapidly effective

- **in bacteremia, peritonitis, and other bacterial infections as of postoperative wounds, and abscesses, when the organism is susceptible to Furadantin**
- **in severe genitourinary tract infections when the patient is unable to take Furadantin per os**

EATON LABORATORIES

NORWICH, NEW YORK

OFFICE OF THE MEDICAL DIRECTOR

Dear Doctor:

For your postoperative or severely ill patients unable to take antibacterial medication by mouth, Eaton Laboratories announces the availability of FURADANTIN INTRAVENOUS SOLUTION.

Furadantin I.V. is proving highly effective in refractory bacterial infections such as bacteremia and peritonitis, and other bacterial infections as of postoperative wounds and abscesses, when the organism is susceptible to Furadantin. In addition, Furadantin I.V. provides an important alternate route of administration for treating genitourinary tract infections in patients unable to take medication by mouth.

The results of clinical studies indicate that Furadantin Intravenous Solution should be tried in certain bacterial infections, refractory to other medicaments, when caused by organisms sensitive to Furadantin. In 75 extra-urinary tract infections including bacteremia, peritonitis, pneumonia, osteomyelitis and abscesses, 34% were cured with Furadantin Intravenous Solution, and an additional 45% were significantly improved.

Side reactions similar to those with oral Furadantin have been encountered, but no serious side effects have been observed in either adults or children.

Furadantin Intravenous Solution not only fills a long-felt need in the treatment of refractory urinary tract infections, but offers new hope in selected, severe systemic infections; even in those which have failed to respond to all other drugs. We are confident that Furadantin I.V. will play an important role in the treatment of your hospitalized patients with severe infections.

Sincerely,

Paul F. MacLeod, M.D.
Medical Director

FURADANTIN I.V.

FURADANTIN I.V. in severe urinary tract infections

No. Cases	Cured	Improved	Failed
71	37 (52%)	28 (39%)	6 (8%)

FURADANTIN I.V. in extra-urinary tract infections

	No. Cases	Cured	Improved	Failed
Peritonitis	6	3 (50%)	2 (33%)	1 (16%)
Bacteremia	23	12 (52%)	6 (26%)	5 (22%)
Postoperative Wound Infection	18	4 (22%)	11 (61%)	3 (16%)
Others (pneumonia, meningitis, osteomyelitis, otitis media, etc.)	28	7 (25%)	15 (53%)	6 (21%)
Total	75	26 (34%)	34 (45%)	15 (20%)

In the following representative cases of urinary tract and extra-urinary tract infections—cases ranging from "severe" to "hopeless"—intravenous administration of Furadantin achieved clinical and bacteriologic cure or marked improvement in a high percentage. Often, a wide variety of antibiotics and sulfonamides had failed to control the infection.

Case Summaries

Sex; Age; Disease Treated	Causative Bacterium	Coexisting Disorder
M; chronic cystitis, pyelonephritis	Ps. aeruginosa in urine	---
F; chronic pyuria with fever	E. coli in urine	---
F; 39; pyelonephritis	Ps. aeruginosa in urine	Staghorn calculus, right
M; 79; bacteremia	E. coli in urine	Post-transurethral resection
F; pyuria, probable bacteremia	A. aerogenes in urine. Blood culture–neg.	Post-panhysterectomy
M; pyelitis, probable bacteremia, chills	E. coli, Ps. aeruginosa	Bilateral renal calculi
Bacteremia	Blood culture positive	Psychosis

FURADANTIN I.V.

Furadantin I.V. Dosage	Result of Treatment	Remarks
180 mg. daily, 3 days	Cured	Resistant to broad spectrum antibiotics and sulfonamides. In 3 days, afebrile; urinary frequency, urgency gone, urine culture negative.
180 mg. daily, 4 days	Cured	Resistant to penicillin and sulfonamides. In 4 days, "afebrile and infection cleared," urine culture negative.
60 mg. q. 8 h., 3 days	Cured	Organism resistant in vitro to Furadantin. Changed to oral form after 3 days on I.V.
360 mg. q. 8 h. for 3 doses, then 180 mg. b.i.d., 2 days	Cured	36 hours post-op. temp. 106.4°. Remission of fever 16 hours after starting Furadantin I.V. Negative urine culture in 5 days.
180 mg. b.i.d., 3½ days	Cured	Antibiotics for 2 weeks. Added oral Furadantin 4 days. Patient semi-comatose when Furadantin I.V. started. Afebrile in 24 hours. Urine culture sterile at 14th day.
180 mg. q.i.d., 5 days	Cured	When Furadantin I.V. started temp. 104°. In 24 hours, temp. 99°. Previous treatment included penicillin, streptomycin and sulfonamide for 5 days each. Patient discharged on oral Furadantin for 5 days. Returned to clinic with negative urine.
180 mg. daily, 2 days	Inconclusive, blood culture negative	"Patient had been resistant to penicillin and streptomycin." Chlortetracycline given intercurrently with Furadantin I.V.

Sex; Age; Disease Treated	Causative Bacterium	Coexisting Disorder
M; empyema and post-surgical wound infection	Pseudomonas sp.	Pulmonary TB, pneumonectomy
M; 75; acute pyelonephritis	None isolated from blood or urine but gross pus in urine	Prostatectomy month before
F; 77; cystitis, atypical pneumonia	(Not stated)	Diabetes mellitus
F; furunculosis	M. pyogenes var. aureus	Post-pyelonephritis
M; 62; recurrent gross hematuria, pyuria	Proteus sp. in urine	Benign hypertrophic prostate
F; 69; peritonitis, bacteremia	E. coli in peritoneal fluid. Proteus sp. in blood	Cancer of colon with perforation, resection
M; 28; peritonitis, bacteremia	Proteus sp. in peritoneal fluid and blood	Ulcerative colitis, obstruction at ileostomy and perforation of small intestine. Resection of perforation and revised ileostomy. Shock
M; 76; pyelonephritis, cystitis	Proteus sp., A. aerogenes in urine	Bilateral renal calculi, uremia
3 weeks old infant; meningitis	E. coli in spinal fluid and urine	---

Furadantin I.V. Dosage	Result of Treatment	Remarks
180 mg. daily, 3 days	Improved	Previous streptomycin and INAH, pneumonectomy. Empyema and wound infection with Pseudomonas. After Furadantin I.V. temp. normal, wound improved. Continued on oral Furadantin.
180 mg. b.i.d., 2 days	Cured	Temp. 103° reduced to normal, urine clear and patient discharged in 2 days. ". . . without Furadantin I.V. . . . probably would have died."
180 mg. daily, 3 days	Cured	Penicillin-dihydrostreptomycin 5 days previous. Temp. 104.4° to normal 24 hours after Furadantin I.V. instituted.
180 mg. daily, 3 days	Markedly improved	Continued elevation in temp. (100-101°) for 10 weeks in spite of intensive antibiotic therapy. Temp. dropped slowly to normal on Furadantin I.V. and no new furuncles developed.
180 mg. daily, 3 days	Improved	Previous sulfonamide treatment 7 days. Bacterium resistant to all tested drugs, slightly sensitive to Furadantin. Temp. normal in 3 days. Followed with oral Furadantin 6 days. TUR following day. Uneventful post-op.
600 mg. daily, 4 days	Cured	Sensitive to chloramphenicol and Furadantin. Furadantin blood level 6-12.5 gamma/cc. Temp. subsided in 24 hours. Culture sterile in 4 days and no drainage. Patient discharged in 2 weeks.
600 mg. daily, 5 days	Cured	Sensitive to chloramphenicol and Furadantin. Furadantin blood level 12.6 to 14.2 gamma/cc.
240 mg. daily, 4 days	Cured	Oral Furadantin ineffective. With Furadantin I.V., cultures became sterile. Furadantin blood levels 2.9 to 6.2 gamma/cc.
3.3 mg./Kg. q. 12 h. for 5 doses	Cured	Fever 2 days. Received antibiotics and sulfonamides. Temp. 103° became normal in 16 hours following institution of Furadantin I.V. and remained so for duration of hospitalization.

FURADANTIN *Intravenous Solution*

DOSAGE AND ADMINISTRATION: Furadantin Intravenous Solution contains 0.6% Furadantin, dissolved in polyethylene glycol 300. Each 10 cc. ampule contains 60 mg. of Furadantin. The solution is sterile and must be dissolved aseptically in a sterile diluent prior to use.

The recommended diluent is 5% dextrose solution. Furadantin Intravenous Solution is compatible with normal saline and ⅙ M sodium lactate solutions, but these should be used only when definitely indicated because of the possibility of further disturbing an already upset electrolytic balance. Administer as an intravenous drip at a rate indicated for the patient's general condition and age. The suggested dosage is 5 to 7 mg. per Kg. body weight (2.2 to 3.1 mg./lb.) per 24 hours in 2 divided doses. The single dose of Furadantin Intravenous Solution for the average adult is 30 cc. (3 ampules or 180 mg.) in at least 500 cc. of diluent. If tolerated, this is repeated so that 2 such doses (360 mg.) are given over 24 hours and continued for 7 days, if necessary. Following are average dosage schedules:

Weight of Patient	*Size of Single Dose*	*Minimal Amount of Diluent*
120 lbs. or over (54 Kg.)	30 cc. (3 amp.) = 180 mg.	500 cc.
80 to 120 lbs. (36-54 Kg.)	20 cc. (2 amp.) = 120 mg.	350 cc.
40 to 80 lbs. (18-36 Kg.)	10 cc. (1 amp.) = 60 mg.	175 cc.

In urinary tract infections, the intravenous form may be replaced by the oral dosage form of Furadantin when sufficient improvement has resulted and patient can take medication orally.

SIDE REACTIONS: Nausea or emesis may occur occasionally. These are often minimized by a decrease in dose rate. Sensitization occurs rarely in the form of urticaria or an erythematous, maculopapular rash. This may be controlled by discontinuing treatment immediately and employing the usual measures such as epinephrine, antihistaminics or adrenocorticosteroids. Occasionally patients may show minor side reactions such as headache or malaise. No stomatitis, colitis, proctitis, anal pruritus, monilial superinfection, staphylococcic enteritis or renal, hepatic or hemic toxicity have been reported.

With intravenous administration, it is important to be alert to the possibility of central nervous system effects such as muscular twitching or spasticity. Should this occur, calcium gluconate should be administered intravenously and Furadantin discontinued. Adequate amounts of vitamin B complex and vitamin C should be supplied to the patient on intravenous Furadantin therapy.

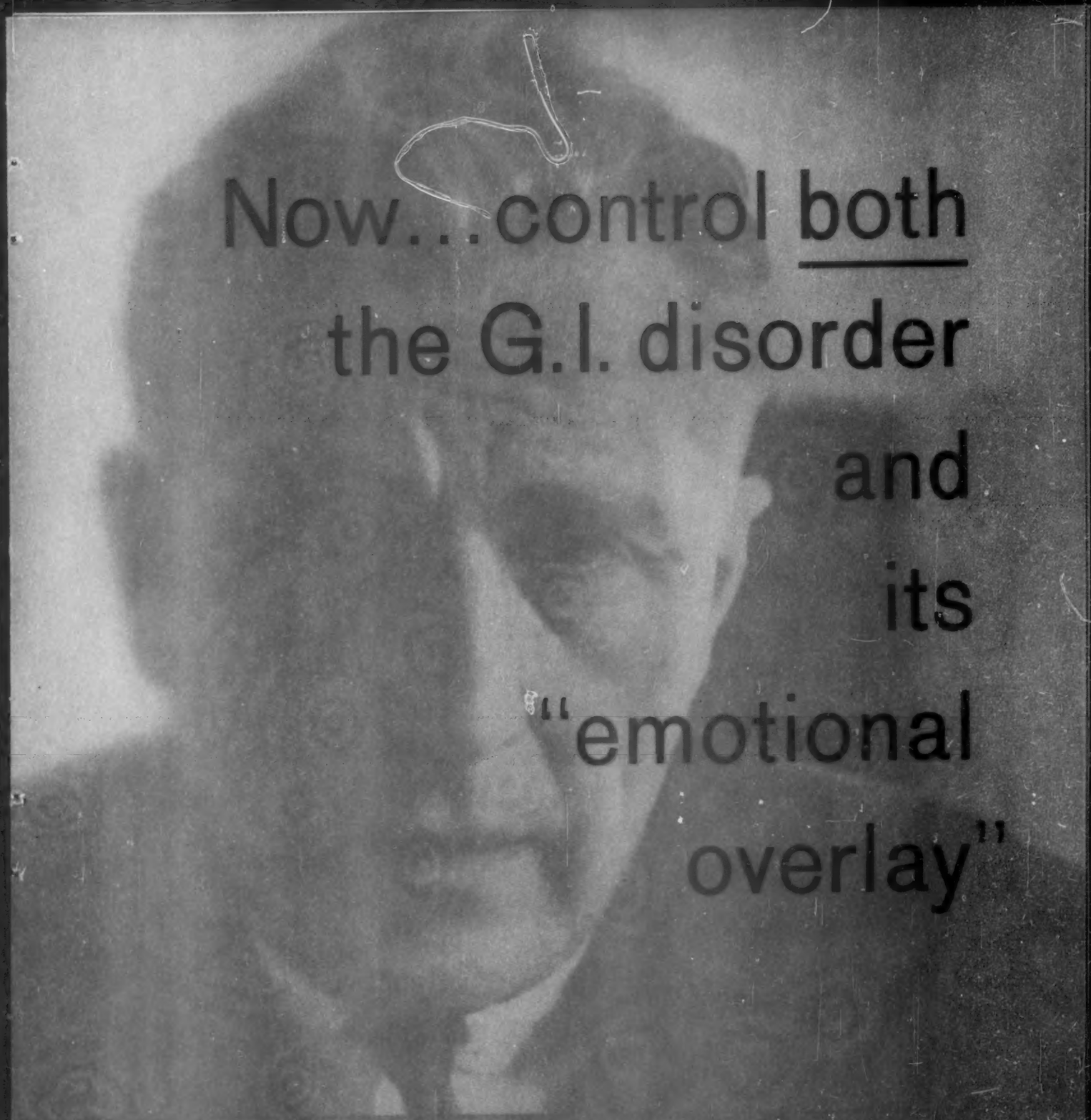
SUPPLIED: Sterile 10 cc. ampules (60 mg. Furadantin each), box of 12.

NOTE: Furadantin Sensi-Discs (100 mcg.) for sensitivity testing are available from the Baltimore Biological Laboratories. Materials and instructions for serial-tube dilution tests may be obtained from the Medical Director of Eaton Laboratories. To simplify sensitivity testing with Furadantin and to provide maximum reproducibility and reliability, Eaton Laboratories has prepared a new booklet, "Bacterial Sensitivity Testing with Furadantin and Furacin," copies of which may also be obtained by writing to the Medical Director.

For oral administration in the treatment of genitourinary tract infections: Furadantin tablets, 50 and 100 mg.; Furadantin Oral Suspension, 25 mg. per 5 cc. tsp.

NITROFURANS—*a new class of antimicrobials—neither antibiotics nor sulfonamides*

PRODUCTS OF EATON RESEARCH—EATON LABORATORIES, NORWICH, N. Y.



Now...control both
the G.I. disorder
and
its
"emotional
overlay"

PATHIBAMATE*

Now... control both

the G.I. disorder

and

its

"emotional

overlay"

PATHIBAMATE*

PATHIB

combines **Meprobamate** *(400 mg.):*

Widely prescribed tranquilizer-muscle relaxant. Effectiveness in anxiety and tension states clinically demonstrated in millions of patients. Meprobamate acts only on the central nervous system. Does not increase gastric acid secretion. It has no known contraindications, can be used over long periods of time.[1,2,3]

with **Pathilon** *(25 mg.):*

An anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of G.I. tract disorders. In a comparative evaluation of currently employed anticholinergic drugs, PATHILON ranked high in clinical results, with few side effects, minimal complications, and few recurrences.[4]

Now...with **PATHIBAMATE**...*you can control disorders of the digestive tract and the "emotional overlay" so often associated with their origin and perpetuation...without fear of barbiturate loginess, hangover or addiction. Among the conditions which have shown dramatic response to* **PATHIBAMATE** *therapy:*

DUODENAL ULCER • GASTRIC ULCER • INTESTINAL COLIC
SPASTIC AND IRRITABLE COLON • ILEITIS • ESOPHAGEAL SPASM
ANXIETY NEUROSIS WITH G.I. SYMPTOMS • GASTRIC HYPERMOTILITY

AMATE

Comments on PATHIBAMATE *from clinical investigators*

- "I find it easy to keep patients using the drug continuously and faithfully. I feel sure this is due to the desirable effect of the tranquilizing drug."[5]

- "The results in several people who were previously on belladonna-phenobarbital preparations are particularly interesting. Several people volunteered that they felt a great deal better on the present medication and noted less of the loginess associated with barbiturate administration."[6]

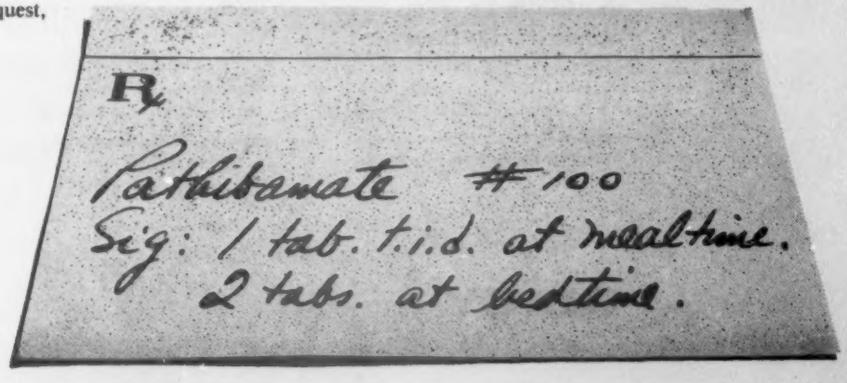
- PATHIBAMATE..."will favorably influence a majority of subjects suffering from various forms of gastrointestinal neurosis in which spasmodic manifestations and nervous tension are major clinical symptoms."[7]

- "In the patients with functional disturbances of the colon with a high emotional overlay, this has been to date a most effective drug."[5]

References: 1. Borrus, J. C.: *M. Clin. North America,* In press, 1957. 2. Gillette, H. E.: *Internat. Rec. Med. & G. P. Clin.* 169:453, 1956. 3. Pennington, V. M.: *J.A.M.A.,* In press, 1957. 4. Cayer, D.: Prolonged Anticholinergic Therapy of Duodenal Ulcer. Am. J. Dig. Dis. 1:301-309 (July) 1956. 5. McGlone, F. B.: Personal Communication to Lederle Laboratories. 6. Texter, E. C., Jr.: Personal Communication to Lederle Laboratories. 7. Bauer, H. G. and McGavack, T. H.: Personal Communication to Lederle Laboratories.

Supplied: Bottles of 100 and 1000

Administration and Dosage: 1 tablet three times a day at mealtimes and 2 tablets at bedtime. Full information on PATHIBAMATE available on request, or see your local Lederle representative.



LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

specifically for reduction of overweight

PRELUDIN®

(brand of phenmetrazine hydrochloride)

"...a highly effective and safe appetite suppressant..."[1]

Based on clinical reports, PRELUDIN produces more than twice the weight loss achieved by patients receiving a placebo.[2] It is singularly free of tendency to produce serious side actions, as well as stimulation.[1-3] PRELUDIN imparts a feeling of well-being that encourages the patient to cooperate willingly in treatment.[1-3]

The reduced incidence of side actions with PRELUDIN makes losing weight more comfortable for the average patient, facilitates treatment of the complicated case and frequently permits its use where other anorexiants are not tolerated.[3]

Recommended Dosage: One tablet two to three times daily one hour before meals. Occasionally smaller dosage suffices. On theoretical grounds, PRELUDIN should not be given to patients with severe hypertension, thyrotoxicosis or acute coronary disease.

(1) Holt, J. O. S., Jr.: Dallas Med. J. 42:497, 1956. (2) Gelvin, E. P.; McGavack, T. H., and Kenigsberg, S.: Am. J. Digest. Dis. 1:155, 1956. (3) Natenshon, A. L.: Am. Pract. & Digest Treat. 7:1456, 1956.

PRELUDIN® (brand of phenmetrazine hydrochloride). Scored, square, pink tablets of 25 mg. Under license from C. H. Boehringer Sohn, Ingelheim.

GEIGY Ardsley, New York

77857

M.D.: Mr. R. A. has left home! Gone back to job; arthritic pain and restriction of activity improved. Feeling tops. Thanks to wonderful medicine you Rx'd.
–Gratefully, WIFE.

Sterane®
brand of prednisolone

Most active anti-rheumatic, anti-allergic, anti-inflammatory corticoid. White, scored 5 mg. tablets (bottles of 20 and 100) and pink, scored 1 mg. tablets (bottles of 100).

Pfizer **PFIZER LABORATORIES** Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York

calmer days . . . more restful nights

beginning first day of treatment

Each Nembu-Serpin Filmtab combines 30 mg. Nembutal Calcium and 0.25 mg. reserpine.

Abbott

filmtab Nembu-Serpin

• Filmtab—Film coated tablets, Abbott • Nembutal—Pentobarbital, Abbott

NEW SANBORN
MODEL 300
VISETTE
electrocardiograph

. . . full diagnostic accuracy in "brief case" size

Growing *use* of the ECG in cardiovascular work means more *locations* in which 'cardiograms are being run: in your office . . . at your patient's home . . . in hospital heart stations, laboratories, wards. This immediately focuses attention on instrument *portability*—and the obvious value of the new Sanborn Model 300 VISETTE.

For the first time—in "brief case" size—is *everything* needed to take a 'cardiogram of full clinical accuracy. This remarkable new *transistorized* direct writer incorporates all the best features of earlier Sanborn instruments developed over the past 33 years—*plus* extremely light weight (18 pounds) and small size (12⅜" x 10½" x 5⅞") made possible by original design and modern electronic components. New in the "300", too, are such operating advantages as *fully* automatic, "one hand" Instomatic action; automatic "push button" grounding; even simpler chart loading; and interlock switch to prevent closing cover with power on.

The doctor with the active cardiac practice will particularly appreciate these VISETTE features; but *wherever* this modern ECG is used, "convenience" will be the characteristic by-word. Ask your Sanborn Representative for full VISETTE information, and a demonstration in your office, of this modern, moderately priced instrument.

The established Sanborn Model 51 Viso-Cardiette is still available for those who prefer a larger, heavier (34 lbs.) instrument—$785, delivered.

SANBORN COMPANY
175 WYMAN STREET, WALTHAM 54, MASS.

Orientation Therapy . . . to remove the psychogenic overlay when unusual emotional stress complicates the menopausal picture

Give your patient the advantage of extra relief from anxiety and tension as well as the physical and mental benefits of "Premarin."

"Premarin" is specific for the alleviation of symptoms of declining ovarian function. It improves general metabolism, stabilizes the vasomotor system, and imparts an added "sense of well being." Meprobamate, through a selective action on the central nervous system, promotes muscular relaxation, relieves anxiety and apprehension, and promotes normal sleeping habit.

Suggested dosage: One tablet three times daily in 21-day courses with a rest period of one week. Dosage should be adjusted to individual requirements.

Supplied: Each tablet contains 0.4 mg. conjugated estrogens equine ("Premarin") and 400 mg. meprobamate, available in bottles of 60 and 500 tablets.

To remove the psychogenic overlay . . .

Meprobamate reduces tension, lessens irritability and restlessness, promotes more restful sleep and generalized muscle relaxation.

(Borrus, J. C. P.: J.A.M.A. 157:1696 [Apr. 30] 1955.)

To treat the basic estrogen deficiency . . .

"Premarin" supplements declining endogenous estrogen levels and provides prompt symptomatic relief of distressing symptoms plus a gratifying "sense of well being."

NEW

"PREMARIN"® WITH MEPROBAMATE

Conjugated Estrogens (equine) with Meprobamate

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

5752

NEW SANBORN MODEL 300 VISETTE electrocardiograph

. . . full diagnostic accuracy in "brief case" size

Growing *use* of the ECG in cardiovascular work means more *locations* in which 'cardiograms are being run: in your office . . . at your patient's home . . . in hospital heart stations, laboratories, wards. This immediately focuses attention on instrument *portability*—and the obvious value of the new Sanborn Model 300 VISETTE.

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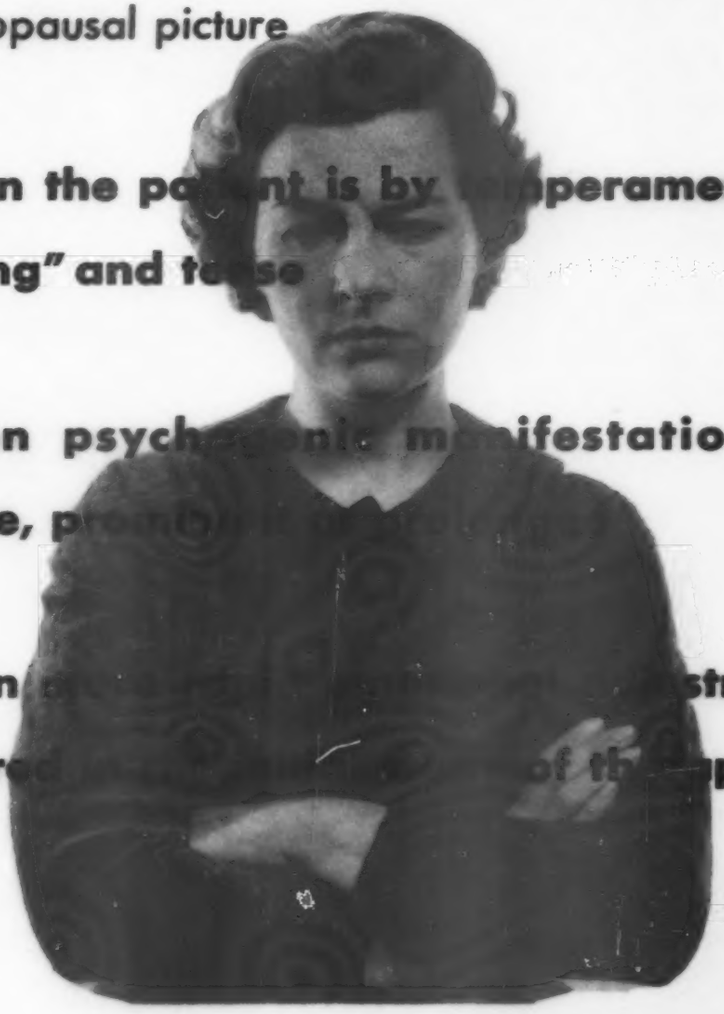
SANBORN COMPANY
175 WYMAN STREET, WALTHAM 54, MASS.

Orientation Therapy . . . to remove the psychogenic overlay when unusual emotional stress complicates the menopausal picture

- **when the pa nt is by perament "high strung" and t se**
- **when psych nic m ifestations are acute, p**
- **when stment is desir of th py**



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NEW

"PREMARIN"® WITH MEPROBAMATE

Conjugated Estrogens (equine) with Meprobamate

5733 **Ayerst Laboratories** • **New York, N. Y.** • **Montreal, Canada**

Ayerst

On the Utilization

of Oatmeal Carbohydrate

IN DIETARY MANAGEMENT, virtually regardless of the adjustment to be made, oatmeal proves remarkably valuable. It is low in sodium, low in purines, low in inert residue, high in protein, notable for its vitamin and mineral content, yet not excessive in calories.

One of the distinguishing characteristics of oats is its relatively lower content of carbohydrate and its higher content of protein, when compared with other whole-grain cereals.[1] An important feature of the carbohydrate of oatmeal is its mode of utilization by the body.

Because it consists mainly of slowly available polysaccharides with relatively minor amounts of dextrins and simple sugars, the carbohydrate of oatmeal does not tend to cause a sudden, sharp increase in blood sugar. Instead, the complex carbohydrate molecules gradually release glucose into the blood stream and thus provide energy on a more sustained basis. Oatmeal is therefore logically recommended as an excellent breakfast dish for diabetics.[2]

The carbohydrate content of oats is almost completely digested and utilized. Cellulose, or cellulose-like material, representing only about 2 per cent of rolled oats in the dry form, provides a gelatinous residue which serves advantageously as nonirritant bulk in the lower intestine.

Whether eaten for therapeutic reasons during illness or for a good sturdy breakfast every day, oatmeal and milk (skim or whole) assures high biologic quality protein, vitamins, and essential minerals, in addition to ease of nutritional utilization.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

1. Kent-Jones, D.W.: Modern Cereal Chemistry, ed. 3, The Northern Publishing Co., Liverpool (1939).

2. Heupke, W., and Kolb, A.: Mechanism of the Beneficial Action of Alimentation of Oats in Diabetes, Deutsche Ztschr. Verdauungeskr. *13*:111 (1953).

The Quaker Oats Company
CHICAGO

designed to

control anxiety

in Arthritis, Asthma, Allergic Dermatoses

with

lower corticoid dosage

the original tranquilizer-corticoid

Ataraxoid*

prednisolone and hydroxyzine

provides the emotional tranquilizer, ATARAX® (hydroxyzine) and the preferred corticoid, STERANE® (prednisolone) • control of emotional factors by tranquilization enhances response to the corticoid for greater clinical improvement • often permits substantial reductions in corticoid dosage, accompanied by reduction of hormonal side effects • confirmed by marked success in 95% of 1095 cases of varied corticoid indications[1]

ATARAXOID *now written as*

Ataraxoid 5.0

5 mg. prednisolone, 10 mg. hydroxyzine hydrochloride, in green, scored tablets. Bottles of 30 and 100.

and now available as **NEW**

Ataraxoid 2.5

2.5 mg. prednisolone, 10 mg. hydroxyzine hydrochloride, in blue, scored tablets. Bottles of 30 and 100.

and **NEW**

Ataraxoid 1.0

1.0 mg. prednisolone, 10 mg. hydroxyzine hydrochloride, in orchid, scored tablets. Bottles of 100.

formerly Ataraxoid
NOW written **Ataraxoid 5.0**

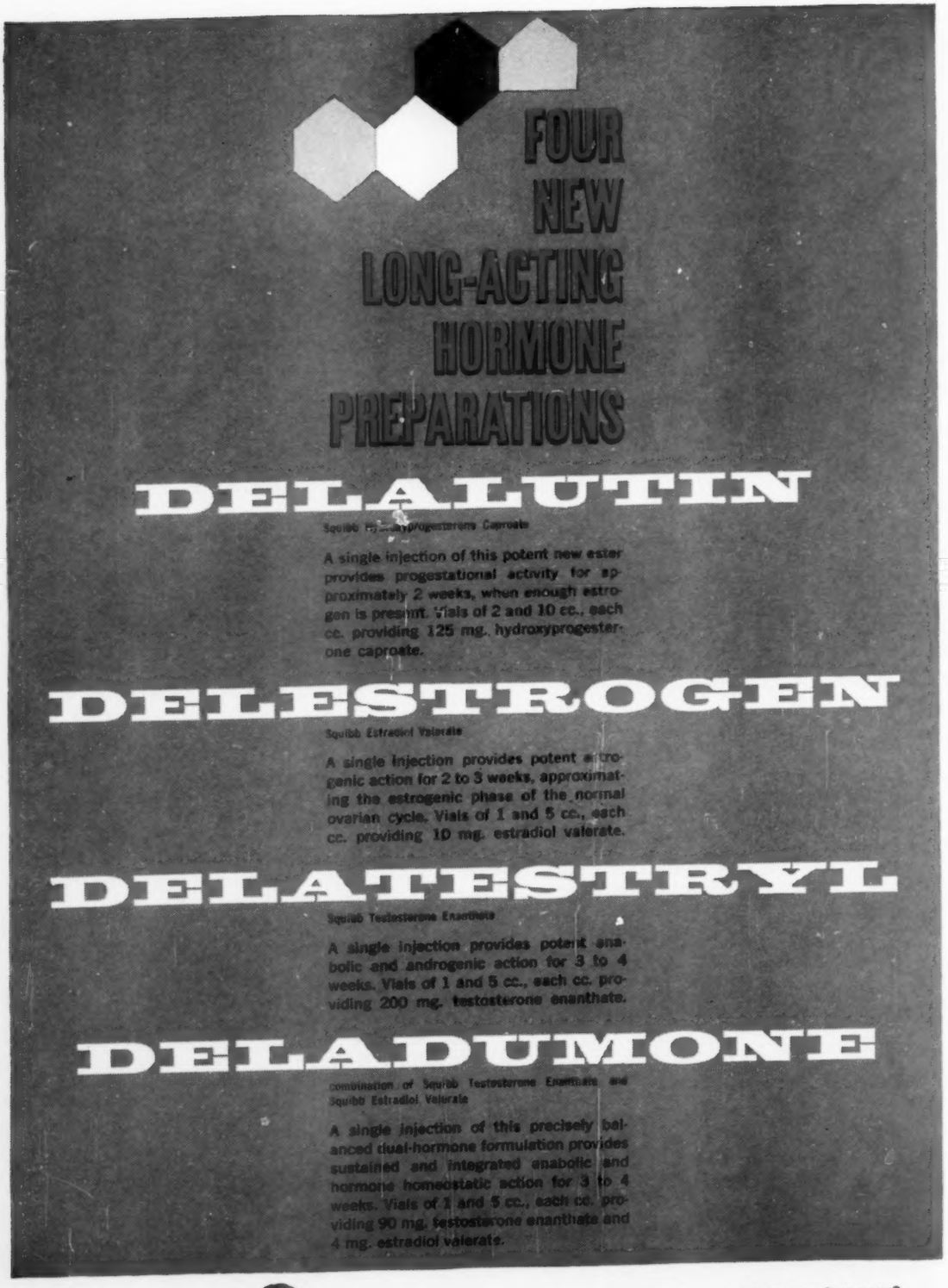
advantages: (1) greater flexibility of dosage (2) effective tranquilization permits lower corticoid dosage

1. Personal communications

*Trademark

PFIZER LABORATORIES *Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York*

Pfizer


FOUR
NEW
LONG-ACTING
HORMONE
PREPARATIONS
DELALUTIN
Squibb Hydroxyprogesterone Caproate
A single injection of this potent new ester provides progestational activity for approximately 2 weeks, when enough estrogen is present. Vials of 2 and 10 cc., each cc. providing 125 mg. hydroxyprogesterone caproate.
DELESTROGEN
Squibb Estradiol Valerate
A single injection provides potent estrogenic action for 2 to 3 weeks, approximating the estrogenic phase of the normal ovarian cycle. Vials of 1 and 5 cc., each cc. providing 10 mg. estradiol valerate.
DELATESTRYL
Squibb Testosterone Enanthate
A single injection provides potent anabolic and androgenic action for 3 to 4 weeks. Vials of 1 and 5 cc., each cc. providing 200 mg. testosterone enanthate.
DELADUMONE
combination of Squibb Testosterone Enanthate and Squibb Estradiol Valerate
A single injection of this precisely balanced dual-hormone formulation provides sustained and integrated anabolic and hormone homeostatic action for 3 to 4 weeks. Vials of 1 and 5 cc., each cc. providing 90 mg. testosterone enanthate and 4 mg. estradiol valerate.

SQUIBB SQUIBB QUALITY—THE PRICELESS INGREDIENT

DELALUTIN®, DELESTROGEN®, DELATESTRYL®, AND DELADUMONE® ARE SQUIBB TRADEMARKS

in severe hypertension dramatic response

nictitating membrane of unanesthetized dog before administration of Ecolid

membrane of same dog eight hours after administration of 2 mg./kg. Ecolid shows dramatic ganglionic blocking effect[1]

Potent, orally and parenterally effective ganglionic blocking agent, **Ecolid**® has dramatically reversed the course of severe hypertension in some patients, and has prolonged their lives. It produces a longer lasting, smoother and more consistent and predictable response than either pentolinium or hexamethonium. However, as with all ganglionic blocking agents, the patient must be carefully managed. Before instituting treatment with **Ecolid** it is advised that the physician be thoroughly familiar with this drug's effects as well as side effects. Complete literature may be obtained from the Medical Service Division, CIBA, Summit, New Jersey.

SUPPLIED: TABLETS (Rotocotes), 10 mg. (orange), 25 mg. (ivory) and 50 mg. (pink). PARENTERAL SOLUTION: *Ampuls*, 1 ml., 5 mg. per ml.

ECOLID® chloride (chlorisondamine chloride CIBA)
ROTOCOTES® (compressed, dry-coated tablets CIBA)

1. Plummer, A.J., Trapold, J.H., Schneider, J.A., Maxwell, R.A., and Earl, A.E.: J. Pharmacol. & Exper. Therap. 115:172 (Oct.) 1955.

CIBA
SUMMIT, N. J.

2/3451MK

Against Pathogen & Pain

in urinary tract infections

Azo Gantrisin combines the single, soluble sulfonamide, Gantrisin, with a time-tested urinary analgesic - in a single tablet.

Prompt relief of pain and other discomfort is provided together with the wide-spectrum antibacterial effectiveness of Gantrisin which achieves both high urinary and plasma levels so important in both ascending and descending urinary tract infections.

Each Azo Gantrisin tablet contains 0.5 Gm Gantrisin 'Roche' plus 50 mg phenylazo-diamino-pyridine HCl. Gantrisin® - brand of sulfisoxazole

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THE AMERICAN JOURNAL OF MEDICINE
49 West 45th Street **New York 36, New York**

Orinase Prescription Information

Dosage: Patients responsive to Orinase may begin therapy as follows:

First day
3 Gm.

Second day
2 Gm.

Third day
1 Gm.

Usual maintenance dose 1 Gm.
(must be adjusted to patient's response)

To change from insulin to Orinase:
If previous insulin dosage was
less than
40 u./day . . . reduce insulin 30% to 50% immediately; gradually reduce insulin dose if response to Orinase is observed.

more than
40 u./day . . . reduce insulin 20% immediately; carefully reduce insulin beyond this point if response to Orinase is observed. In these patients, hospitalization should be considered during the transition period.

Caution: During the initial "test" period (not more than 5 to 7 days), the patient should test his urine for sugar and ketone bodies three times daily and report to his physician daily. For the first month, he should report at least once weekly for physical examination, blood sugar determination, and white cell count (with differential count, if indicated). After the first month, the patient should be seen at least once a month, and the above studies carried out.

It is especially important that the patient, because of the simplicity and ease of administration of Orinase, does not develop a careless attitude ("cheating" on his diet, for example) which may result in serious consequences and failure of treatment.

Supplied: In 0.5 Gm. scored tablets, bottles of 50.

Complete literature available on request.

Upjohn

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KALAMAZOO, MICHIGAN

now available...

← save

Upjohn

the new oral antidiabetic agent

ORINASE*

Used investigationally in more than 18,000 patients! *(Tolbutamide, Upjohn)*

Ready for your prescription now. Orinase is now available in all leading prescription pharmacies. But please, before you prescribe this exciting new drug, be sure you understand its limitations.

Indications. Orinase is most likely to benefit the patient in whom the diabetes is relatively mild and stable, is not adequately controlled by dietary restrictions alone, and developed sometime after the age of 30 years.

Contraindications. Orinase is contraindicated in patients with 1) diabetes of the types known variously as juvenile, growth-onset, unstable, or brittle; 2) a history of diabetic coma; 3) diabetes complicated by ketosis, acidosis, coma, fever, severe trauma, gangrene, Raynaud's disease, or serious impairment of renal or thyroid function; 4) hepatic dysfunction; and 5) diabetes adequately controlled by dietary restriction.

Effects. In patients with a satisfactory response to Orinase, the blood sugar falls, glycosuria diminishes, and such symptoms as pruritus, polyuria, and polyphagia disappear. It is *not* a substitute for insulin. And it requires the same adherence to basic principles of diabetes control as does insulin, e.g., dietary regulation; tests for glycosuria and ketonuria; hygiene; exercise; instruction of the patient to recognize and counteract impending hypoglycemia, to follow rigidly directions regarding diet and continuing use of the drug and to report immediately to the physician any feeling of illness. Extreme care must be taken during the transition period to avoid ketosis, acidosis, and coma.

Side effects. To date, the most serious side effect is hypoglycemia, which may occur occasionally and is most likely to occur during the transition period from insulin to Orinase. Other untoward reactions to Orinase are rare, usually of a nonserious nature, and tend to disappear on adjustment of dosage, e.g., gastrointestinal disturbances, headache, variable allergic skin manifestations, and alcohol intolerance.

Clinical toxicity. Aside from an occasional hypoglycemia, Orinase appears to be remarkably free of gross clinical toxicity. There is no evidence of crystalluria or other untoward effects on renal function, or of hepatotoxicity. Except for a rare leukopenia of mild degree, which has been reversible (in some instances, even under continued therapy), there have been no adverse effects on hematopoietic function.

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can be managed conservatively

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Squibb Chloral Hydrate

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"...no proof that it is deleterious to the heart..."

"The psychiatrist often finds it the agent of choice..."
"...much less likely to produce mental excitement..."

"...frequently the favorite of the dermatologist..."
"...skin reactions from it are uncommon..."

Current Concepts in Therapy: Sedative-Hypnotic Drugs.
II. Chloral Hydrate. New England J. Med. 255:706 (Oct. 11) 1956.
adults: 1 or 2 7½ gr. capsules or 1 or 2 teaspoonfuls of
Noctec Solution 15 to 30 minutes before bedtime.
children: 1 or 2 3¾ gr. capsules or ¼ to 1 teaspoonful
of Noctec Solution 15 to 30 minutes before bedtime.
7½ and 3¾ gr. capsules, bottles of 100.
Solution, 7½ gr. per 5 cc. tsp., bottles of 1 pint.

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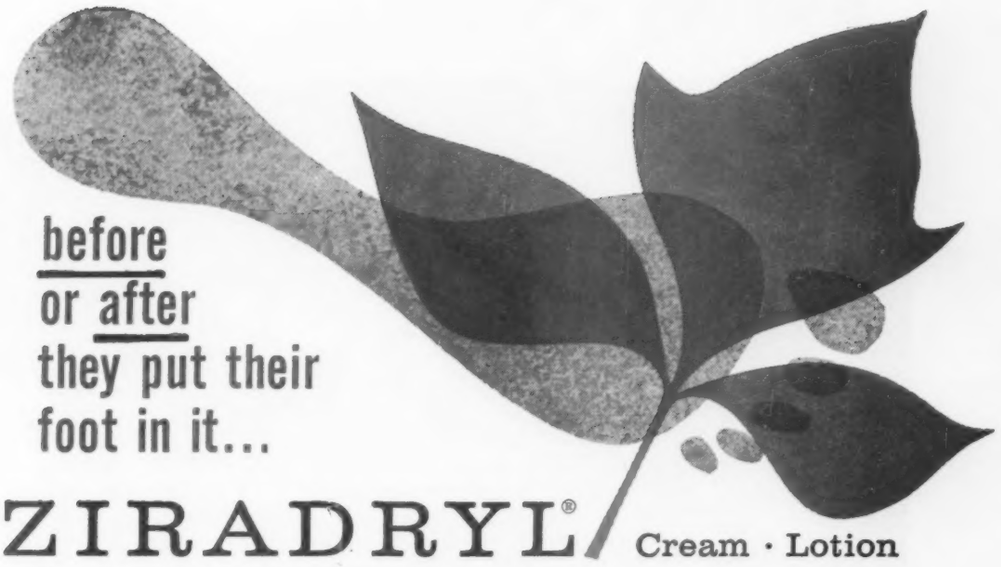

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or after
they put their
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PRACTICAL DIET THERAPY

ALMOST every physician makes use of nutritional principles and practice in his daily work. This is the point of view underlying The American Journal of Clinical Nutrition which conceives of nutrition as an adjunct in the total care of every patient. Cutting across arbitrary boundaries of specialties, nutrition is used by internist, surgeon, pediatrician and obstetrician alike. It has been called "the cornerstone of preventive medicine, the handmaiden of curative medicine, and the responsibility of every physician."

As part of our objective of integrating modern concepts of nutrition into clinical practice, The American Journal of Clinical Nutrition features a series of authoritative articles in the field of diet therapy. Written by eminently qualified experts in the field these concise, up-to-date reviews are prepared for the clinician in practice. The series has attracted considerable interest and in order to make this conveniently available for reference and use the publishers have decided to reprint it in a combined form. This seminar on practical nutrition presents a point of view rarely found in traditional textbooks or monographs. A glance at the wide gamut of topics listed in the table of contents will clearly illustrate the point previously made—that nutrition is part and parcel of all therapy. This anthology is presented, therefore, as a guide to better practice which is, after all, the goal of all medical workers.

80 Pages—12 Charts

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Each Multiple Compressed Tablet of MEPROLONE provides the inseparable antiarthritic, antirheumatic benefits of:

1. *Prednisolone buffered*—the newest and most potent of the "predni-steroids" for prompt relief of joint pain and arrest of the destructive inflammatory process.

2. *Meprobamate*—the newest and safest of the muscle-relaxant tranquilizers for profound relaxation of skeletal muscle in spasm.

Tolerance to this combination is good because there is little likelihood of sodium retention, potassium depletion or gastric distress with buffered prednisolone, and meprobamate rarely produces significant side effects in therapeutic dosage.

An additional important therapeutic benefit, often overlooked, stems from the tranquilizing action of meprobamate. This component of MEPROLONE relieves mental tension and anxiety so often manifest in arthritics, making them more amenable to other rehabilitation measures.

INDICATIONS: A wide variety of conditions, in which four symptoms predominate: *a*) inflammation *b*) muscle spasm *c*) anxiety and tension *d*) discomfort and disability; i.e., rheumatoid arthritis, rheumatoid spondylitis (Marie-Strümpell disease), Still's disease, psoriatic arthritis, osteoarthritis, bursitis, synovitis, tenosynovitis, myositis, fibrositis, fibromyositis, neuritis, acute and chronic low back pain, acute and chronic primary and secondary fibrositis and torticollis, intractable asthma, respiratory allergies, allergic and inflammatory eye and skin disorders (as maintenance therapy in disseminated lupus erythematosus, periarteritis nodosa, dermatomyositis and scleroderma).

Therapeutic benefits of MEPROLONE compared with traditional antiarthritics.

	relieves pain	suppresses inflammation	relaxes muscle	eases anxiety	imparts sense of well-being
Salicylates	✓	✓			
Muscle relaxants			✓[1]		
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Steroids	✓	✓			✓
MEPROLONE	✓	✓	✓	✓	✓

1. Meprobamate is the only tranquilizer with muscle-relaxant action.

SUPPLIED: Multiple Compressed Tablets in bottles of 100 in two formulas as follows: MEPROLONE-1—1.0 mg. of prednisolone, 200 mg. of meprobamate and 200 mg. of dried aluminum hydroxide gel. MEPROLONE-2—provides 2.0 mg. of prednisolone in the same formula.

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THE ONLY

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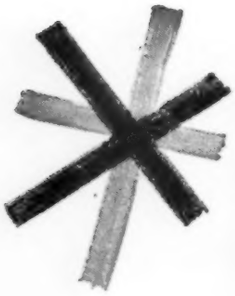

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Supplied in 5-cc vials, each cc containing 40 U.S.P. units of corticotropin adsorbed on zinc hydroxide (2.0 mg zinc/cc)

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mineral-vitamin-hormone supplement

prophylaxis for concomitants of aging
to promote good health and vitality later

- vitamins and minerals to help maintain cellular function
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- steroids to stimulate metabolism

*Stare, F. J.: Nutritional Problems of Advancing Age, *Bull. New York Acad. Med.* **32**:284, 1956.

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THE PICTURE OF COMFORT... ALL THROUGH THE PREGNANCY
if she's blue at breakfast...
BONADOXIN®
(brand of Meclizine HCl and Pyridoxine HCl)
stops morning sickness
Controlled studies indicate that BONADOXIN relieves symptoms-quickly-in 9 of every 10 gravida. Tolerance is excellent.
Prescribe: One tablet at bedtime. Severe cases, one tablet at bedtime, one on arising. In tiny pink-and-blue tablets, bottles of 25 and 100. ℞ only.
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prescribe STORCAVITE®
Phosphate-free calcium, iron, 10 essential vitamins, 8 important minerals.
Usually 3 tablets daily, with meals. In bottles of 100.
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by children and mothers / convenient dosage regimen / excellent taste / wide acceptance by children and mothers

for sustained
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'ROCHE'

therapeutic blood levels
for 24 hours —
with only two oral doses

LIPO GANTRISIN 'ROCHE'

assures adequate blood levels around-the-clock . . . with only two doses daily

Description: Lipo Gantrisin provides the wide antibacterial spectrum of Gantrisin in a special vehicle. In this free-flowing, readily digestible vegetable oil emulsion the action of the drug is prolonged. With each dose therapeutic blood and urine levels of highly soluble Gantrisin are maintained over a period of twelve hours.

Each teaspoonful (5 cc) of Lipo Gantrisin contains the equivalent of 1 Gm of Gantrisin. Lipo Gantrisin can be employed without alkalies and without danger of renal blocking or secondary fungus growth.

Indications: Systemic and urinary infections due to streptococci, staphylococci, pneumococci, H. influenzae, K. pneumoniae, meningococci, E. coli, B. proteus, B. pyocyaneus, A. aerogenes, B. paracolon, and Alcaligenes fecalis.

Dosage: Teaspoonfuls every 12 hours

Children:	
20 lbs	½
40 lbs	1
60 lbs	1½
80 lbs	2
Adults:	
	3

Caution: the usual precautions in sulfonamide therapy should be observed.

If required, the initial dose may be twice the amount of subsequent doses. Treatment should be continued until temperature has been normal for at least 48 hours.

Supplied: Bottles of 4 and 16 oz.

Lipo Gantrisin® Acetyl—brand of acetyl sulfisoxazole in vegetable oil emulsion

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PREDNISOLONE
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PARACORTOL*
PREDNISOLONE
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PREDNISOLONE

Supplied:
5 mg. and 2.5 mg. scored tablets; bottles of 30 and 100

THREE TO FIVE TIMES MORE EFFECTIVE THAN HYDROCORTISONE

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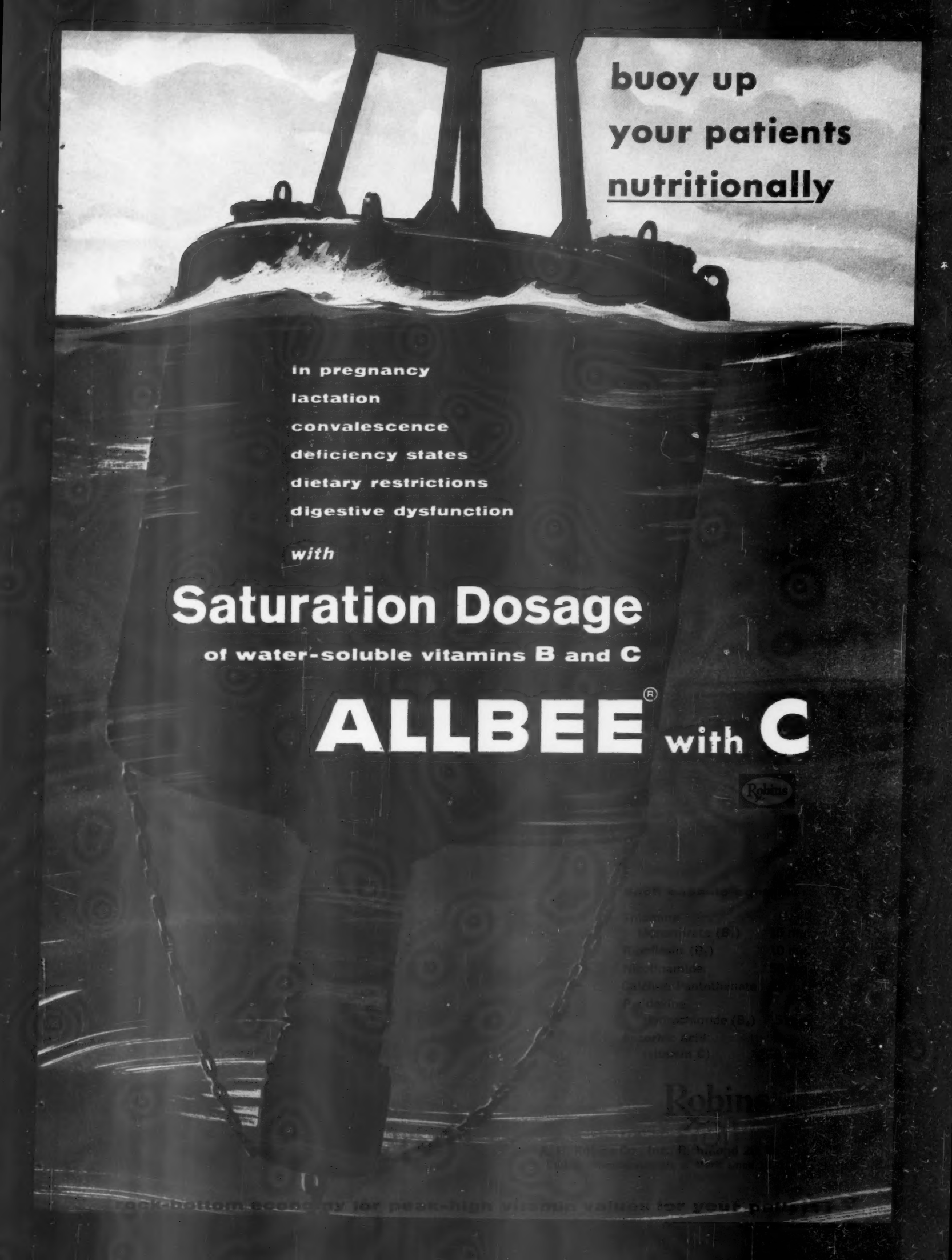
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...an important, new aid

for reduction

of elevated cholesterol

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TRADEMARK

(ABBOTT'S SAFFLOWER OIL EMULSION)

PALATABLE, NEW EMULSION

OFFERS THE HIGHEST PERCENTAGE

OF UNSATURATED FATTY ACIDS

OF ALL VEGETABLE OILS

Over recent years, the study of atherosclerosis has strongly suggested that its control may be aided through the correction of hypercholesteremia. It has been repeatedly observed, further, that the substitution of highly unsaturated fats for saturated fats reduces elevated cholesterol blood levels in certain individuals.

With the highest percentage of unsaturated fats of all edible vegetable oils, Abbott's new safflower oil emulsion, SAFF, is thus indicated in the management of hypercholesteremia. Significantly, safflower oil, while representing a uniquely concentrated natural source of linoleic acid, contains the *lowest* percentage of saturated fatty acids. The following table shows the relation between fatty acid composition and biological activity in a number of food fats:

ESSENTIAL FATTY ACID ACTIVITY OF VARIOUS FOOD FATS

	Linoleic Acid	Other Polyenic Acids	Saturated Acids	Biological* Activity
Safflower oil	74.5%	—	6.6%	78.8%
Soybean oil	53.3%	7.8%	13.2%	62.4%
Corn oil	56 %	—	13 %	—
Cottonseed oil	49.6%	1.3%	26 %	48.5%
Sesame oil	41 %	—	13 %	28.2%
Linseed oil	12.5%	52.1%	9.6%	11.9%
Olive oil	12 %	—	12 %	—
Lard	5.6%	1.3%	43 %	6.9%
Tallow (beef)	0.9%	1 %	53 %	1.5%
Butter	2 %	1.7%	47 %	1.1%
Margarine	5.8%	—	23 %	—
Coconut oil	1.9%	—	82 %	1.1%

*Relative potency for curing essential fatty acid deficiency in rats when linoleic acid is assigned a value of 100. Thomassen, H. J.: "Biological Standardization of Essential Fatty Acids", International Rev. of Vit. Res., 25:62, 1953.

In relating diet to blood cholesterol, one typical study[1] included five groups of human subjects, whose controlled diets alternated from large percentages of unsaturated fats to identical percentages of saturated fats. Conclusions drawn were that plasma cholesterol increased with ingestion of saturated fats whereas a diet of unsaturated fats consistently *decreased* plasma cholesterol. Such studies strongly suggest that unsaturated fat can be of value in the regulating of hypercholesteremia.

Clinical and Laboratory Findings

In promoting the growth, well-being, and survival of experimental animals, safflower oil (SAFF) has proved much more effective than hydrogenated vegetable oil. Indeed, in the laboratory,[2] atheroma-like changes have been produced in rabbits on a purified ration containing hydrogenated vegetable oil. *No* such lesions resulted from the administration of comparable quantities of safflower oil.

SAFF finds ready acceptance in the management of conditions where weight-gain is desirable—such as undernutrition or convalescence. Moreover, from studies, such as those of Deuel and Reiser,[3] it is evident that unsaturated fats have a special value in nutrition—one not shared by any other kind of food.

Opportunity For Immediate Study

SAFF's true worth can best be demonstrated through studies in which it is administered to patients with hypercholesteremia, including those with atherosclerosis, or those having a tendency toward it. Again, in individuals with coronary disease, the effect of controlled essential fatty acid intake on cholesterol and lipid blood levels will be of particular significance.

In many patients, substitution of SAFF for saturated fat in the diet will provide a demonstrable lowering of blood cholesterol.

With a light butterscotch flavoring, SAFF is highly palatable right from the spoon. Mixes easily with most liquids as well as with a number of foods.

SAFF's recommended dosage is five tablespoons daily. Available in one-pint-bottles.

Abbott

REFERENCES: 1. Beveridge, J. M. R.; Connell, W. F.; and Mayer, G. A.: "Dietary Factors Affecting the Level of Plasma Cholesterol in Humans: The Role of Fat." Canad. J. Biochem. & Physiol. 34:441-55, May, 1956. 2. Lambert, G. F.; Olson, R. T.; Miller, J. P., Jr.; and Frost, D. V.: Laboratory Records, Nutrition Research, Abbott Laboratories, 1956-57. 3. Deuel, H. J. Jr., and Reiser, R.: "The Physiology and Biochemistry of the Essential Fatty Acids." Vitamins and Hormones, Volume 13, pp. 29-70, 1955

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tanphetamin protocolloid complex
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greater therapeutic benefits...
GREATER than any other anorexic you can use...
"Thus, definite benefits resulted in a total of 579 (82.8%) of 699 cases treated."*
less CNS overstimulation...
LESS than any other anorexic you can use...
Only 3.7% of 699 patients on proper dosage schedule exhibited CNS overstimulation with Synatan (tanphetamin)*

the smoothest amphetamine compound you can use

To serve your patients today—call your pharmacist for any additional information you may need to help you prescribe Seco-Synatan and Synatan.

For prescription economy, prescribe Synatan and Seco-Synatan in 50's.

*Garrett, T. A.: Clin. Med. 3: 1185 (Dec.) 1956.

each **Synatan** tabule contains tanphetamin (dextro-amphetamine tannate) 17.5 mg.

Seco-Synatan contains Synatan 17.5 mg. and secobarbital 35.0 mg.

dosage: One or two tabules at 10:00 a.m. for all day control.

IRWIN, NEISLER & CO. DECATUR ILLINOIS.

CLINICAL COLLOQUY

My patients complain that
the effect of the pain tablet I prescribe
often wears off in less than 3 hours.

***Why not try the new codeine derivative
that's combined with APC
for faster, longer-lasting pain relief?***

You mean something that
doesn't require repeat dosage so often?

***Yes—it's called Percodan.®
It not only works in 5 to 15 minutes but
one tablet sustains its pain-relieving effect
for 6 hours or longer!***

How about side effects?

***No problem. For example,
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Sounds worth trying—what's the average adult dose?

One tablet every 6 hours. That's all.

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*U.S. Pat. 2,628,185. PERCODAN contains salts of dihydrohydroxycodeinone and homatropine, plus APC. May be habit-forming. Available through all pharmacies.

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for skeletal muscle spasm

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Brand of Orphenadrine HCl

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Effective

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*Trademark of Brocades-Stheeman & Pharmacia
U.S. Patent No. 2,567,351. Other patents pending.

In addition to its spasmolytic effect, Disipal evokes a mildly euphoric response, particularly valuable in the Parkinsonian patient.

Disipal is nonsoporific. Continuous therapy for as long as 44 months produced no serious ill effect, no tolerance.

In 480 cases of Parkinsonism (arteriosclerotic, postencephalitic, and idiopathic), 50 investigators reported good to excellent results in 286 (59%), and fair in 97 (20.2%).

In 120 cases of other types of muscle spasm, good results were obtained in 59 (49.1%) and fair results in 24 (20.1%). Side effects are minimal.

Dosage: Initially 1 tablet (50 mg.) t.i.d. In combination with other spasmolytic drugs, dosage is titrated to meet individual needs.

Riker
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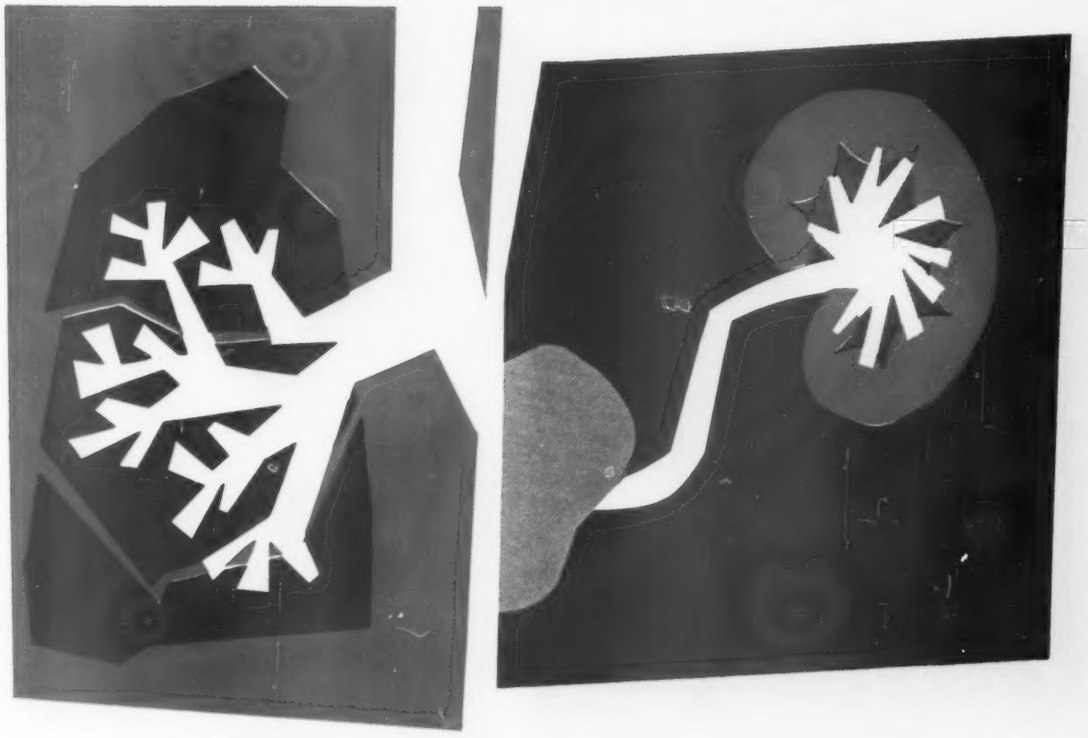

for prompt clinical response in many common infections
especially those of the urinary and respiratory tracts

prescribe **Terfonyl**

Squibb Triple Sulfas
Trisulfapyrimidines

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1. Lehr, D.: Modern Med. 23:111 (Jan. 15) 1955.

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*Goodhart, H. S.: Vitamin Therapy Today, *M. Clin. North America* 40:1473, 1956.

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The American Journal of Medicine

VOL. XXIII JULY, 1957 No. 1

Editorial

The Concept of Relative Bone Marrow Failure

RELATIVE bone marrow failure implies that the marrow may produce a normal or greater than normal number of cells in response to cell loss or destruction, but that it is not able to keep pace with demand even though the rate of destruction is one for which a normally functioning marrow could compensate completely. A rough analogy may be made to the heart of an elderly patient with coronary artery disease which does well under ordinary demands but fails in the presence of hyperthyroidism. The concept of relative bone marrow failure has been developed during the last few years as information about the rates of red blood cell formation and destruction has accumulated. So far, because technics for studying the balance between the destruction of white blood cells and platelets have not been discovered, this concept can be applied only to the anemias but there is every reason to believe that it is applicable to some of the leukopenias and thrombocytopenias as well. In the past, clinicians have found it difficult to understand why certain anemias are associated with cellular or hyperplastic marrows when there is no morphologically detectable evidence of increased hemolysis or loss; the anemias were regarded as being due to poor production of cells. Why, then, was not the marrow hypocellular? Arrested maturation or a breakdown in the mechanism of delivery of cells to the peripheral blood were offered as explanations but there was usually no histologic basis for these suggested derangements. More recent evidence indicates that in many instances there is significant acceleration of red cell destruction, which is detectable only with technics for measuring corpuscular survival; the marrow may be making cells actively, and so be cellular, or even hyperplastic, but production lags behind need.

Before specific examples of relative bone marrow failure are cited, brief comment should be made about the methods used for measuring formation and destruction of cells, and about the maximum rate of compensation attainable by normal marrow.

The circulating life span of red corpuscles, established as being normally about 110 to 120 days, can be measured with reasonable accuracy by either the Ashby method of differential agglutination or by tagging transfused cells with radioactive chromium [*1*]. Other satisfactory technics have been used (such as, tagging heme with C^{14} by administering C^{14} tagged glycine), but these two have been employed most widely. The Cr^{51} method is easier to use. This method makes it possible to follow the survival of the patient's own cells in his own circulation, it avoids the potential errors which might result from cross transfusions if isosensitization to minor blood groups occurred, but it suffers from the disadvantages that the Cr^{51} seems to be eluted from the cells, not always perhaps at a constant rate, and may possibly injure the corpuscular stroma. With proper precautions and with careful interpretation of the data, however, the information about cellular destruction with either method is good enough for clinical interpretation.

The methods for estimating red blood production are much less satisfactory. Reticulocyte counts, estimates of the nucleated red cells per

[1] MOLLISON, P. L. and VEALL, N. The use of the isotope ^{51}Cr as a label for red cells. *Brit. J. Haematol.*, 1: 62, 1955.

unit volume of marrow, determination of the plasma iron turnover per day and of the utilization of tracer amounts of Fe^{59} for hemoglobin synthesis provide only rough approximations at best [*2–4*]. Yet, when used in combination, they do provide information which serves as a useful index of the rate of erythropoiesis, valuable for comparative purposes even though quantitatively not exact.

A well nourished bone marrow which becomes hyperplastic in response to blood loss or hemolysis can produce red cells at about six to eight times the normal rate [*5*]. In a patient with chronic hemolytic disease, therefore, it is possible for a normal erythrocyte count to be maintained even though the average red cell survival time becomes as short as sixteen to twenty days. If the survival time decreases to less than this range, hemolytic anemia invariably results because even the healthy, hyperplastic marrow is no longer able to compensate. By the same token, a healthy marrow could compensate with relative ease for a hemolytic rate three times the normal (corpuscular survival of forty days). If on the other hand, it was able to respond to this stimulus by only doubling its production rate, a moderate anemia would result and a state of relative bone marrow failure could be said to exist. Here is what would happen to the peripheral red cell count and to the total circulating red cell mass under these circumstances:

(1) A hypothetic patient has a normal red blood cell count of 5,000,000 cells per cu. mm. and a circulating erythrocyte mass of 2,400 ml. With a corpuscular life span of 120 days, he would be destroying and making 20 ml. of erythrocytes per day.

(2) A disease now develops which causes his red cells to survive for only forty days so he begins to destroy 20×3 or 60 ml. of cells per day. Because the disease also affects his marrow, he is able to increase erythropoiesis to only 40 ml. per day. The corpuscular mass and count will gradually decrease until the circulating red cell mass is down to 1,600 ml. At this level, which is two-thirds of the original, the volume of erythrocytes destroyed per day at a survival rate of forty days will be $1,600 \div 40$ or 40 ml. A new equilibrium will now be set because the marrow is capable of producing this quantity of new cells per day. If the total blood volume has remained constant, the peripheral red cell count will now be 3,330,000 per cu. mm.

The anemia in this hypothetic situation has resulted from increased hemolysis and the failure of the marrow to compensate for a normally compensatable rate of destruction—relative bone marrow failure. In many instances, if the survival time of the red cells is determined and it is known to be accelerated but more than twenty days, it is possible to make a calculation similar to the one cited to establish the fact that the marrow must be producing cells at a normal or greater than normal rate. The presence of relative bone marrow failure can thus be recognized even though direct measurement of cellular production has not been made.

Among the most complete data are those for the anemia which is found in association with cancer. Many but not all patients with cancer show a shortened red cell survival time, which is due presumably to an extracorpuscular hemolytic factor; reference to the many studies which establish this fact are available in two recent papers [*6,7*]. There are fewer evaluations of production rate but these studies indicate that the anemia in patients with cancer is characterized usually by a failure of the marrow to compensate fully for an increased rate of red cell destruction, whether the destruction is mild or severe [*6,7*]. In a few instances the anemia may be caused solely by deficient red cell production. Similarly, in leukemia there is frequently a hemolytic component to the anemia [*4,6,8,9*]

[2] Bothwell, T. H., Callender, Sheila, Mallett, Barbara and Witts, L. J. The study of erythropoiesis using tracer quantities of radioactive iron. *Brit. J. Haematol.*, 2: 1, 1956.

[3] Giblett, E. R., Coleman, D. H., Pirzio-Biroli, G., Donohue, D. M., Motulsky, A. G. and Finch, C. A. Erythrokinetics: quantitative measurements of red cell production and destruction in normal subjects and patients with anemia. *Blood*, 11: 291, 1956.

[4] Berlin, N. I., Lawrence, J. H. and Elmlinger, P. J. Recent advances in the knowledge of total red cell volume, production and destruction. *Blood*, 12: 147, 1957.

[5] Crosby, W. H. and Akeroyd, J. H. The limit of hemoglobin synthesis in hereditary anemia. *Am. J. Med.*, 13: 273, 1952.

[6] Miller, A., Chodos, R. B., Emerson, C. P. and Ross J. F. Studies of the anemia and iron metabolism in cancer. *J. Clin. Invest.*, 35: 1248, 1956.

[7] Hyman, G. A. and Harvey, J. L. The pathogenesis of anemia in patients with carcinoma. *Am. J. Med.*, 19: 350, 1955.

[8] Berlin, R. Red cell survival studies in normal and leukemic subjects. *Acta Med. Scandinav.*, Suppl. 252, 1, 1951.

[9] Ross, J. F., Crockett, C. J., Jr. and Emerson, C. P. The mechanism of anemia in leukemia and malignant lymphoma. *J. Clin. Invest.*, 30: 668, 1951.

which is compensated for only in part by accelerated erythropoiesis [*4,6,10*]. Recognition that the marrow has this degree of competence, however, has therapeutic implication in patients with chronic lymphocytic leukemia or the malignant lymphomas because the anemia may frequently be corrected if the abnormal hemolysis is controlled by steroid therapy or by splenectomy [*11*].

When anemia exists in patients with cirrhosis of the liver, the red cell survival time has been found to be shortened due to an extracorpuscular hemolytic process and to be proportional to the severity of the anemia [*12*]. Hemoglobin production usually did not exceed two to three times the normal rate but occasionally increased enough, when nutrition was improved or when alcohol was withdrawn, to bring about partial correction of the anemia even though the rate of hemolysis seemed unchanged. The anemia of rheumatoid arthritis is likewise due to a combination of shortened erythrocytic life span and failure of the marrow to respond adequately to the stress of the anemia. In many instances, the hemolytic component is very mild so that subnormal production of cells seems to be the major responsible factor. In other patients with corpuscular life spans as short as forty days, the marrow appears to be making more than the normal number of cells although it fails to speed up production enough to compensate for the hemolysis [*13*]. The anemia of infection is associated with a moderate decrease in red cell survival time, averaging only 27 per cent in one series of cases [*14*]. Whether cell formation is always depressed to levels less than the normal or may at times merely fail to increase enough to correct the hemolytic component is not yet clear.

In some patients with autoimmune hemolytic disease (acquired hemolytic anemia) it seems entirely possible that the antibodies responsible for peripheral destruction of cells may also inhibit erythropoiesis enough to prevent the compensation which might otherwise occur, although studies on the only two patients for whom data have been published fail to support that contention [*3*]. Measurements of cell production and survival time in the same patient are not available for disseminated lupus erythematosus, sarcoidosis and many other diseases in which splenomegaly occurs; relative bone marrow failure may well be found to be of importance in the pathogenesis of anemic states associated with some of these disorders as well.

Uremia seems to be a clear exception. While a hemolytic component is frequently present in the anemia of uremia, erythropoiesis is apparently always depressed [*15,16*]. The same statement may be made for refractory or hypoplastic anemias although accelerated destruction occasionally is associated with only mildly inadequate red cell formation so that splenectomy may effect marked improvement even though a normal count is not restored [*3,17,18*].

Whether or not the same considerations will apply to leukopenic and thrombocytopenic states is of course unknown. Technics are now available for studying the circulatory life span of platelets [*19*] but production cannot yet be evaluated. The problem with regard to leukocytes is even more complicated since white blood cells spend a portion of their functionally active life in tissues outside the circulatory bed. It seems reasonable to predict, however, that the same considerations will be found to hold—that marrow affected by a disease process will be able to respond with increased production of

[10] Huff, R. L., Hennessy, T. G., Austin, R. E., Garcia, J. F., Roberts, B. M. and Lawrence, J. H. Plasma and red cell iron turnover in normal subjects and in patients having various hematopoietic disorders. *J. Clin. Invest.*, 29: 1941, 1950.

[11] Reinhard, E. H. and Loeb, V., Jr. Dyssplenism secondary to chronic leukemia or malignant lymphoma. *J. A. M. A.*, 158: 629, 1955.

[12] Jandl, J. H. The anemia of liver disease: observations on its mechanism. *J. Clin. Invest.*, 34: 390, 1955.

[13] Ebaugh, F. G., Jr., Peterson, R. E., Rodnan, G. P. and Bunim, J. J. The anemia of rheumatoid arthritis. *Med. Clin. North America*, 39: 489, 1955; *Clin. Res. Proc.*, 2: 55, 1954.

[14] (*a*) Bush, J. A., Ashenbrucker, H., Cartwright, G. E. and Wintrobe, M. M. The kinetics of iron metabolism in the anemia associated with chronic infection. *J. Clin. Invest.*, 35: 89, 1956. (*b*) Wintrobe, M. M. Clinical Hematology, 4th Ed., p. 588 (1956).

[15] Loge, J. P., Lange, R. D. and Moore, C. V. Characterization of the anemia of chronic renal insufficiency. *J. Clin. Invest.*, 29: 830, 1950.

[16] Joske, R. A., McAlester, J. M. and Prankerd, T. A. J. Isotope investigations of red cell production and destruction in chronic renal disease. *Clin. Sci.*, 15: 511, 1956.

[17] Loeb, V., Moore, C. V. and Dubach, R. The physiologic evaluation and management of chronic bone marrow failure. *Am. J. Med.*, 15: 499, 1953.

[18] Doan, C. A. and Wright, C. S. Primary congenital and secondary acquired splenic panhematopenia. *Blood*, 1: 10, 1946.

[19] Leeksma, C. H. W. and Cohen, J. A. Determination of the life span of human blood platelets using labelled diisopropylfluorophosphonate. *J. Clin. Invest.*, 35: 964, 1956.

these formed elements when they are being destroyed or lost with abnormal rapidity, but at a rate in many instances less than that possible for an unhampered marrow.

What has been called here relative bone marrow failure has been designated by others as "functional inadequacy of the marrow" or "relative hypofunction." The term is of no consequence so long as the physiologic principle is understood. The bone marrow can fail in two ways: (1) by failing to produce a normal number of cells (true failure), or (2) by failing to increase its production as much as would a normal marrow in response to a given stimulus (relative failure). Fluctuations in the severity of the disease affecting the marrow undoubtedly cause swings between true and relative failure. Essentially nothing can be said as yet about the mechanism of the failure: a depressant affect directly on the marrow or on the elaboration of a marrow hormone, like erythropoietin. At least partial clarification will almost certainly come from the tremendous current interest in the latter substance.

The concept of relative bone marrow failure has definite therapeutic implications in some instances; if one knows that the marrow is capable of producing at least a normal number of cells, and if one can accumulate evidence that a significant proportion of the accelerated destruction is occurring in an enlarged spleen, he can proceed to splenectomy with more rationale and confidence. The concept of relative bone marrow failure, however, is probably of most value in bringing about a better understanding of the pathogenesis of erythroid disorders, and of encouraging physicians to think of the marrow in the same functional terms which are now so readily applied to the pulmonary, renal and cardiovascular systems.

CARL V. MOORE, M.D.

Clinical Studies

Further Observations on Patients with Malignant Carcinoid*

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SOME clinical, physiologic and biochemical findings in six patients with metastatic carcinoid tumors were presented in a previous report from this laboratory [*1*]. The major chemical alterations were found to consist of elevated blood levels of serotonin (5-hydroxytryptamine) and a greatly increased urinary excretion of the serotonin metabolite, 5-hydroxyindoleacetic acid (5HIAA). The elevated urinary 5HIAA has now become accepted as a simple method for diagnosis of the disorder [*2*]. Production of large amounts of serotonin by the tumors was shown to require a major utilization of its dietary precursor, tryptophan. Serotonin excess as well as secondary tryptophan deficiency were considered as possible factors in the pathogenesis of the associated clinical syndrome.

Studies have now been carried out in thirteen additional patients. Since the usual clinical manifestations of the disorder have been described, only relevant aspects of additional case histories are presented here. The various aspects of further investigation of the disorder are presented in the section on experimental results in accordance with the following outline:

Measurements of serotonin and 5HIAA
  Blood, urine and cerebrospinal fluid
  The question of "free" serotonin in plasma
  Different vascular sites
  During flushes
  Renal metabolism of 5HIAA
  Carcinoid tumor
Studies with radioactive 5-hydroxytryptophan
  Turnover of serotonin
  Calculation of serotonin pool and tumor mass
Chemical evidence of tryptophan and niacin deficiency
  Low plasma tryptophan levels
  Low excretion of N′-methylnicotinamide
Pharmacologic studies
  Reserpine
  Serotonin "antagonists"
Psychologic evaluation

MATERIALS AND METHODS

Eight patients were hospitalized for these studies at the Clinical Center of the National Institutes of Health. Four were of the original group of six patients studied previously and the details will not be repeated [*1*]. Specimens for analysis in nine additional patients (Cases XI through XIX) were received from elsewhere and available clinical information concerning some of these patients was incomplete.

Serotonin was measured by the methods of Udenfriend, Weissbach and Clark [*3*] and 5HIAA by the method of Udenfriend, Titus and Weissbach [*4*]. Total urinary 5-hydroxyindoles were measured by making quantitative use of the direct color test with nitrosonaphthol [*2*]. The platelets were isolated from 15 to 30 ml. of blood according to the procedure of Dillard, Brecher and Cronkite [*5*]. The platelets were washed three times with 5 ml. of isotonic sodium chloride by resuspension, centrifugation and decantation of the wash fluid. After the final wash the platelets were resuspended in a small volume of the saline solution and aliquots taken for analysis of protein [*6*] and serotonin. All steps in the isolation of platelets required the use of siliconized glassware. The platelet serotonin values were expressed as μg./mg. protein. This procedure obviates the need for platelet counts on the original blood and on platelet suspensions to correct for losses during isolations. "Platelet-free" plasma was obtained in the course of platelet isolation

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or by immediate, rapid centrifugation of the blood sample.

The following method was developed as a simplified assay for serotonin in whole blood containing elevated amounts of serotonin (patients with carcinoid and rabbits): blood is drawn in the same manner as for platelet assay [*5*]; to 1 ml. of blood add 4 ml. water; precipitate proteins by addition of 1 ml. of 10 per cent $ZnSO_4$ and 0.5 ml. of 1 N NaOH; centrifuge and to 1.0 ml. of the supernate add 0.3 ml. of 12 N HCl; read in the spectrophotofluorometer [*7*] at an activating wavelength of 295 mμ and a fluorescence wavelength of 550 mμ. Eighty to 90 per cent of the fluorescence obtained with blood from patients with carcinoid is due to serotonin and the remainder to other 5-hydoxyindoles (mainly 5HIAA). For the determination of 5HIAA in plasma a 2 ml. aliquot was extracted in the manner described for urine [*4*], omitting the 2-4-dinitrophenylhydrazine precipitation and chloroform extraction steps. The extract was then acidified and read in the spectrophotofluorometer as described for assay of serotonin in whole blood.

In the study with radioactive 5-hydroxytryptophan, urine was extracted for 5HIAA by the standard procedure; 1 aliquot was assayed chemically and another counted in a Geiger-Müller counter. To check the results of this procedure similar aliquots were applied to Whatman No. 1 filter paper and chromatograms developed with n-propanol—1 NNH_3 (5:1). Five-HIAA eluted from the paper chromatograms had the same specific activity as obtained by the extraction method.

Plasma tryptophan was measured by the method of Duggan and Udenfriend [*8*]. E. G. McDaniel of the National Institute of Arthritis and Metabolic Diseases kindly carried out the measurements of urinary N′-methylnicotinamide using the method of Huff and Perlzweig [*9*].

CASE REPORTS

Cases I through VI;* see previous publication [*1*]. The patients in Cases I through IV were rehospitalized for additional studies and were known to be alive as recently as August, 1956.

CASE VII. The first admission of a forty-eight year old white woman was for one week in September, 1955, when she complained chiefly of numerous episodes of "blushing" of ten years' duration. Severe attacks were accompanied by facial edema, wheezing and dyspnea. An exploratory laparotomy performed elsewhere in January, 1955, had revealed carcinoid tumors in the liver with the primary site undetermined. Pertinent physical findings included: blood pressure of 120/80 mm. Hg, facial erythema, angiomatous telangiectasia over the nose and malar eminences and a large nodular liver. She was hospitalized again on May 2, 1956, with complaints of weakness, weight loss, severe diarrhea, fever, abdominal pain and swelling of the ankles. The results of physical and laboratory examinations were suggestive of an abscess in the right lower quadrant of the abdomen. Gradual but striking improvement occurred with the use of antibiotics, diuretics and symptomatic measures and she was discharged on July 7, 1956.

CASE VIII. A forty year old white man was hospitalized for three weeks in January, 1956. Aside from a gradual weight loss of 15 pounds since July, 1954, he had felt well until October, 1955, when pain in the right upper quadrant of the abdomen, chills, fever and leukocytosis led to exploratory laparotomy performed elsewhere. The liver was found to be enlarged and studded with metastatic carcinoid nodules. A solitary primary tumor was resected from the terminal ileum and postoperative recovery was uneventful. Pertinent physical findings on admission included: evidence of weight loss, blood pressure of 120/70 mm. Hg, a soft systolic murmur of doubtful significance at the pulmonic area, and a large nodular liver. Two episodes of facial flushing were observed during the period of hospitalization and subsequently flushes occurred approximately once weekly. Complaints during follow-up visits over a three month period consisted of inability to gain weight, frequent gaseous abdominal distention with diarrhea, and intermittent pain over the liver.

CASE IX. A bedridden, fifty-seven year old white woman was hospitalized from February 16, 1956, to March 9, 1956. There was a history of cough, progressive dyspnea and a 40-pound weight loss during the previous two years. An x-ray of the chest in July, 1954, showed several nodular lesions in the left lung and one on the right, interpreted as inoperable metastatic neoplasm. Regression of the lesions followed a course of x-ray therapy. An abdominal operation was performed elsewhere in January, 1955, following an attack of pain in the right lower abdomen. At the time of surgery a mass measuring 8 cm. in diameter was discovered in the mesentery of the ascending colon and traced to an apparent origin in a retrocecal appendix. The appendix and mass were resected. The mass consisted of inflammatory tissue and carcinoid tumor with probable origin in the appendix. A left pleural effusion was discovered in December, 1955, and a biopsy specimen of a left supraclavicular mass was interpreted as showing carcinoid tumor. Pertinent physical findings on admission included: cachexia, air hunger, blood pressure of 150/95 mm. Hg, pulse rate of 110 per minute, a 3 by 3 cm. nodular mass in the left supraclavicular area, diminished expansion of the entire left hemithorax with associated dullness to percussion and diminished breath sounds, resonance to percussion over the sternum, a systolic thrill with a grade 4 murmur obscuring the heart sounds in the second and third intercostal spaces to the left of the

* Case VI has been reported in detail by Daugherty et al. [*10*].

sternum, and a palpable liver. An electrocardiogram showed only low voltage. An x-ray of the chest revealed complete opacification of the left hemithorax, a shift of mediastinal structures to the left and compensatory emphysema of the right lung. Other diagnostic procedures were refused by the patient. The patient died at home on May 15, 1956, and an autopsy was performed on the following day. Residual carcinoid tumor was found adjacent to the appendiceal stump. There were four metastatic lesions in the liver, two in the pancreas, one in the left lung and extensive infiltration by tumor of the upper mediastinum with resultant stenosis of the left main stem bronchus, left pulmonary artery and ascending aorta. The murmur noted clinically was attributed to mechanical stenosis of the left pulmonary artery since the heart and great vessels were normal otherwise. The right lung was emphysematous and the left was atelectatic and suppurative.

CASE X. A forty year old white man was admitted to the hospital on April 29, 1956. In November, 1953, hepatomegaly was discovered on routine examination and an exploratory laparotomy performed in January, 1954, had revealed metastatic carcinoid from an undetermined primary site. He recalled "blushing" easily all his life and having low-grade asthma since he was eighteen years old. During World War II the blushing became persistent but was attributed by physicians to sunburn or "birthmark." Bluish discoloration of the face appeared in 1946. He felt well until August, 1955. Thereafter he noted progressive weight loss, weakness, numerous paroxysms of wheezing controlled by inhalations of isopropylarterenol, intermittent profuse diarrhea and swelling of the legs. Pertinent physical findings on admission included: cachexia; "cyanosis" of the face; erythema of the entire skin surface but most intense on the face, neck and thorax; blood pressure of 110/70 mm. Hg; systolic expansile pulsations of the jugular veins, prolonged expiratory phase of respiration with musical rales on auscultation; grade 2 apical systolic murmur; flaring of the costal margins; a very large spleen and tremendous, nodular liver extending "en masse" to the iliac crests; and edema of the lower legs. The electrocardiogram was compatible with right ventricular hypertrophy. Most interesting of the routine laboratory findings were: serum potassium of 7.0 mEq./L., white blood cell count of 45,000 per cu. mm. with immature leukocytes and nucleated erythrocytes on blood smear, slight anemia and platelet count of 1,900,000 per cu. mm. Sections of bone marrow obtained by trephine biopsy were interpreted as showing a markedly cellular marrow with megakaryocytes and cells of the myeloid series as the predominant cell types, and nests of tumor cells. The peripheral arterial oxygen saturation was 96 per cent. Cardiac catheterization showed a right atrial pressure curve typical of tricuspid insufficiency and the following intravascular pressures: pulmonary artery, 40/20; right ventricle, 42/10 and right atrium, 41/17 mm. Hg. The patient improved with use of digitalis, diuretic measures, blood transfusions and symptomatic therapy and was discharged on June 30, 1956.

CASE XI. A sixty-seven year old white man died on November 7, 1955, seven days after surgical removal of a suppurative appendix and a polypoid carcinoid tumor of the terminal ileum. He had felt well prior to the recent onset of severe pain in the abdomen. The preoperative blood pressure was 150/90 mm. Hg. The findings at postmortem examination included a large duodenal ulcer and carcinoid metastases in the mesentery, liver, spleen, pancreas and lung. Death was attributable to cerebral thrombosis.

CASE XII. A sixty year old white man gave a long history of diarrhea and "psychiatric problems." On examination in February, 1956, flushing of the skin and hepatomegaly were noted but there was no evidence of cardiac involvement. Exploratory laparotomy revealed primary carcinoid of the ileum with extensive metastases to the liver. No other information is available.

CASE XIII. In October, 1954, a fifty-six year old white man underwent surgery for the removal of a carcinoid tumor protruding into the cecum from the terminal ileum. Early in 1956 a metastatic lesion was removed from the soft tissue of the chest wall. The metastatic lesion had a microscopic appearance similar to that of the intestinal tumor but was interpreted by some observers as adenocarcinoma. The patient is feeling well and is said to have no evidence of the "carcinoid syndrome."

CASE XIV. A fifty year old Negro man had an exploratory laparotomy performed in April, 1956, because of persistent vague abdominal distress. X-rays of the entire gastrointestinal tract had been interpreted as showing no abnormalities. A small ulcerating carcinoid tumor was found in the terminal ileum and resected, together with metastases to regional nodes. The retroperitoneal area was "completely filled" with neoplasm and two nodules were seen in the liver. Postoperative recovery was satisfactory.

CASE XV. A twenty-nine year old Negro man was admitted to the hospital in April, 1956, with major complaints of nervousness, excessive sweating and diarrhea of three years' duration. He also suffered from arterial spasm in the extremities when nervous or on exposure to cold. The blood pressure varied from 130/96 to 200/100 mm. Hg. A loud systolic murmur was heard along the left sternal border and a mild degree of pulmonic stenosis was demonstrated by cardiac catheterization. The liver was felt 2 fingerbreadths below the right costal margin. An exploratory laparotomy performed on May 21, 1956, revealed multiple metastases in the liver and a small, ulcerating

nodule in the terminal ileum with a large metastasis in the adjoining mesentery. The primary tumor was excised and had a microscopic appearance typical of carcinoid. Convalescence was satisfactory and improvement occurred with symptomatic measures.

CASE XVI. A sixty-five year old white woman was seen in consultation on July 26, 1956. Her chief complaint was of intermittent severe diarrhea of eight years' duration. Edema of the legs had developed in February, 1956, requiring the use of diuretics. Surgical removal of a carcinoid in the cecal area was performed on November 6, 1952, and metastases were seen in the liver and omentum. She recalled having been told of a heart condition (murmur ?) thirty years ago and of slight cardiomegaly in recent years. On examination she appeared well, the blood pressure was 145/95 mm. Hg, a soft systolic murmur was audible at the cardiac base and a harsh, grade 3 systolic murmur was heard at the apex, the liver was not palpable and there were no other significant findings. Alterations in chest roentgenograms and electrocardiograms were compatible with left ventricular hypertrophy. The major cardiac lesion was considered to be rheumatic mitral insufficiency.

Cases XVII through XIX: the only information available is that the patients had metastatic carcinoid proved histologically.

Comments: The association of vasomotor disturbances, respiratory distress, valvular heart disease and diarrhea with metastatic carcinoid is borne out by these additional case studies. However, it is apparent that more cases are being recognized prior to development of the typical syndrome. One patient (Case IX) succumbed to the mechanical effects of pulmonary and mediastinal metastases before secretion of serotonin was sufficient to produce other symptoms. A frequent complication in patients followed-up for the past two years has been the occurrence of episodic pain over the liver with fever and leukocytosis but negative blood cultures. These episodes usually subside spontaneously and may be due to hemorrhagic necrosis of tumor nodules. Such an attack was the presenting complaint of one patient (Case VIII) and associated abdominal rigidity caused the hepatomegaly to be overlooked until the time of surgery. Whether or not peptic ulcer (Case XI) and "leukemoid reaction" (Case X) are in some way related to excess serotonin production remains to be ascertained.

After two years of clinical experience with the disorder one is impressed particularly by the wide variation in symptomatology and the remarkably prolonged survival. An optimistic outlook is justified despite the presence of signs and symptoms which are considered ominous when due to other types of metastatic neoplasm. The patient may have ample opportunity in his lifetime to consult a variety of medical specialists and hence presents a peculiar type of medical challenge. Intensive clinical study and review of hospital records are necessary to delineate further the natural history of the condition.

EXPERIMENTAL DATA

Measurements of Serotonin and 5HIAA. Knowledge of the exact status of serotonin and its metabolites in different body fluids is of importance in a disorder of this type in attempting to relate each of the clinical manifestations to the chemical disturbance. For example, the suggestion that the right side of the heart is damaged preferentially due to exposure to higher concentrations of serotonin should be amenable to verification by determination of serotonin levels in different vascular sites (*vide seq.*). Actually, the measurement of 5-hydroxyindole compounds in man presents many problems. In few instances do different laboratories use the same methods and often little information is published covering details of the technics. It is not surprising, therefore, that certain discrepancies have appeared. This section of the paper deals with problems of measuring serotonin and 5HIAA in various compartments and discusses the limitations and difficulties of existing methods. Additional findings are presented, some of which are based on newly developed methods (see section on methods).

Blood, urine and cerebrospinal fluid: As shown in Table I, the serotonin content of blood platelets and urinary excretion of 5HIAA in patients with carcinoids were consistently elevated. With the exception of Cases IX, XVI and XVII, in which relatively low levels of 5HIAA were found, the diagnosis of carcinoid was established easily by the rapid screening test [*2*]. Although it was reported previously that serotonin could not be detected in cerebrospinal fluid [*1*], Snow and associates [*11*] apparently were able to measure a significant amount (0.5 μg./ml.) in fluid obtained at the time of necropsy. However, additional analyses of spinal fluid in three patients (Cases IV, VII and X) again revealed no significant amount of serotonin (<0.03 μg./ml.).

Improved methodology has permitted measurement of 5HIAA in the blood of patients with

carcinoid. The values obtained have ranged from 0.2 to 0.8 μg./ml. of plasma.

The question of "free" serotonin in plasma: No serotonin was found in the plasma of the first few patients studied in this laboratory. It was therefore assumed that almost all the circulating serotonin was bound to platelets. Although some free serotonin must exist in the blood of these patients, it was supposed that available methods were inadequate to measure these small amounts. Subsequently, Snow and associates [*11*] reported serotonin levels in "platelet-poor" plasma of 0.05, 0.16 and 0.3 μg./ml. in three patients with carcinoid, employing a bioassay procedure. Since levels of this magnitude are easily measured chemically, this problem was reinvestigated. Values obtained on numerous plasma assays ranged from an insignificant amount (<0.03 μg./ml.) to as high as 2.7 μg./ml. in one instance. However, the meaning of plasma values reported to date is open to question. Since it is impossible to avoid completely the breakage of platelets when plasma is separated from the formed elements of blood, the serotonin which is measured in plasma may be partially accounted for by platelet rupture. On the other hand, it is possible that serotonin which is initially free may actually be adsorbed onto platelets during the preparative procedure. Mindful of these difficulties it is believed that none of the reported values for free serotonin in blood can be considered reliable. That free serotonin does occur in blood is shown by the findings after the administration of reserpine. In this case a serotonin level of 0.5 μg./ml. of plasma was found when the platelet serotonin content was negligible (*vide seq.*).

TABLE I
SEROTONIN IN BLOOD PLATELETS AND 5HIAA IN URINE

Case	Serotonin (μg./mg. platelet protein)	5HIAA (mg./day)
Normal Subjects		
	0.26–0.63*	2–9†
Patients with Carcinoid		
I–VI	1.0 –5.4‡	76–580
VII	1.9	450–680
VIII	5.6	157–192
IX	4.4	14–28
X	0.6§–1.7	368–630
XI	.....	72
XII	1.1	665
XIII	.....	381
XIV	.....	32
XV	.....	77
XVI	1.4	21
XVII	.....	22
XVIII	.....	42
XIX	.....	51

* Range of values in ten normal subjects.
† Range of values in forty subjects without carcinoid.
‡ Converted by multiplication factor of 2 from original values expressed as μg./ml. of blood.
§ Low value attributable to thrombocytosis and difficulties in isolation of platelets due to leukocytosis.

TABLE II
SEROTONIN CONTENT OF WHOLE BLOOD AND PLASMA IN VARIOUS VASCULAR SITES

Case	Serotonin Content	Peripheral Vein (μg./ml.)	Pulmonary Artery (μg./ml.)	Femoral Artery (μg./ml.)
IV	Blood	1.7	1.7	2.3
	Plasma	1.8	1.6	2.3
VIII	Blood	2.0	2.2	2.4
	Plasma	2.3	2.3	2.7
X	Blood	3.0	3.0	3.2

Different vascular sites: It has been suggested [*1,12*] that the predominance of right-sided heart involvement might be related to exposure of the right side of the heart to a higher concentration of free serotonin than the left, due to metabolism of serotonin by the lungs. Apparently, Goble et al. [*12*] were successful in confirming this hypothesis in studies on a single patient using chromatographic technics for serotonin analysis. They reported a plasma serotonin level of 6.2 μg./ml. in the pulmonary artery and 2.2 μg./ml. in the brachial artery. In three previous cardiac catheterization studies reported from our laboratory [*1*] no differences in platelet serotonin level were found between mixed venous and arterial blood but no attempt was made to measure plasma serotonin. Three additional cardiac catheterization studies were performed. As shown in Table II, no significant differences in plasma or whole blood serotonin were found in samples taken from the peripheral vein, pulmonary artery and

femoral artery. Although a pulmonary arteriovenous serotonin difference may exist in the plasma, its demonstration will have to await the development of more reliable methods for separating plasma from the formed elements.

During flushes: Repeated studies have failed to show alterations in the circulating level of either free or platelet-bound serotonin during flushing episodes. However, daily measurements of urinary 5HIAA have seemed to indicate that a greater amount of serotonin was being released during periods of flushing. This was particularly convincing in one patient (Case IV) during two severe flushes lasting seven and ten days, respectively. The daily excretion of 5HIAA rose from control levels of 200–400 mg. to 600–900 mg. during the height of flushing. Over an interval of six weeks following one of these episodes the daily excretion then fell to a low value of 93 mg./day, followed by a gradual return to control levels. Thus, in spite of the absence of a measurable rise in the blood levels of serotonin, it appears that severe flushing, at least, is accompanied by an increased release of serotonin from the tumor.

Renal metabolism of 5HIAA: Since only small amounts of 5HIAA have been available for study, the renal excretory mechanism for this substance could not be studied by ordinary infusion technics. However, this problem is easily studied in patients with carcinoid. The administration of 2.0 gm. of probenecid intravenously in two of these patients was followed by a decrease in the rate of excretion of 5HIAA and an increase in its concentration in plasma; these results imply an active tubular transport mechanism [*13*]. Clearance data in these patients also indicate that 5HIAA is excreted by glomerular filtration and tubular secretion in a manner similar to para-aminohippurate [*14*].

Carcinoid tumor: A carcinoid tumor analyzed previously was found to contain 0.8 mg. of serotonin per gm. of tumor tissue. Additional specimens were obtained at the time of autopsy of two patients (Cases XI and IX). In Case XI the serotonin content of carcinoid metastases in three different organs was as follows: pancreas, 1.0 mg./gm.; liver, 3.0 mg./gm.; and lung, 0.85 mg./gm. In Case IX no significant amount of serotonin was found in a pulmonary metastasis and in the primary tumor adjacent to the appendiceal stump. Tumor from the mediastinum, liver and pancreas contained 0.17, 0.17 and 0.22 mg./gm., respectively. Since the primary tumor in this case was thought to arise from the appendix, it is possible that massive production of serotonin is peculiar to the ileal carcinoid. On the other hand, these low values may be the result of a lapse of twelve hours between the time of death and postmortem examination. Since the rate at which tissue levels of serotonin decline after death is an undetermined variable, it is suggested that meaningful data can be obtained only by using fresh material obtained at the time of surgical procedures. Since serotonin can be measured in tissue by a simple colorimetric procedure, it is suggested that portions of such tumor specimens be frozen routinely for analysis at a later date.

Studies with Radioactive 5-hydroxytryptophan. Since 5-hydroxytryptophan is the immediate precursor of serotonin, administration of this substance in radioactive form provides a means whereby one can label the 5-hydroxyindole pool of the body [*15*]. Eight microcuries of 2-C^{14}-5-hydroxy-DL-tryptophan (15.0 mg.) were given intravenously to a patient (Case II) and the daily urinary excretion and specific activity of 5HIAA were measured for a period of ten days. The excretion of 5HIAA was relatively constant during this time, averaging 350 mg./day. The daily specific activity of 5HIAA (counts per minute per micromole) is plotted as a logarithmic function in Figure 1. The relatively high specific activity of 5HIAA for the first two days may be explained partially by rapid conversion of the "unnatural" form of the amino acid to 5HIAA by D-amino acid oxidase. If one assumes uniform labeling of the 5-hydroxyindole pool and that after the second day the end-product, 5HIAA, is in equilibrium with this pool, the whole body turnover of these compounds can be calculated. Since serotonin comprises the bulk of the total 5-hydroxyindole compounds of the body and only a negligible percentage is present elsewhere than in the tumor, the turnover rate in a patient with carcinoid is in essence an approximation of the turnover of serotonin in the tumor. The slope of the latter part of the curve (Fig. 1) indicates a half-life of five and one-half days. Assuming that the specific activity of 5HIAA is a first order function of time and that the production rate of serotonin is at least equal to the urinary excretion rate of 5HIAA (350 mg./day), then it may be

estimated that the pool size is 2.00 mg.* The magnitude of this pool can be appreciated by the fact that 1 mg. of serotonin produces pharmacologic effects in man when given intravenously. Since the serotonin content of carcinoid tumor tissue is usually in the range of

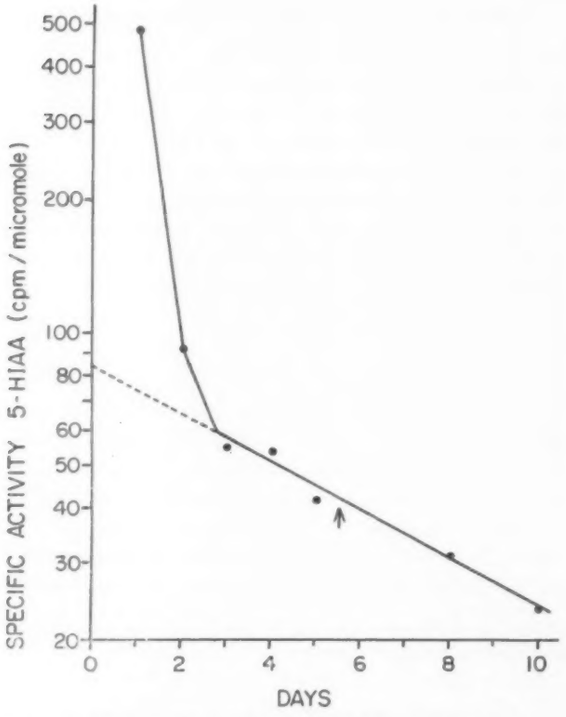

FIG. 1. Daily specific activity of 5HIAA after administration of 2-C^{14}-5-hydroxy-DL-tryptophan. Half-life of five and a half days is indicated by the arrow.

1.0 to 3.0 mg./gm., the estimated carcinoid mass in this patient would range from 1 to 3 kgm. The latter figure is comparable to that which might have been guessed clinically in this patient.

Chemical Evidence of Tryptophan and Niacin Deficiency. As reported previously [7], an important aspect of the metabolic abnormality in the carcinoid syndrome is the conversion of the serotonin pathway from a minor to a major route for the metabolism of tryptophan. It was suggested that secondary tryptophan deficiency, with decreased formation of other products such as protein and niacin, be considered in the pathogenesis of the disorder. Measurements of plasma tryptophan in the fasting state and urinary excretion of N′-methyl-nicotinamide were made to obtain further information on the state of tryptophan and niacin stores in these patients.

TABLE III
FASTING PLASMA LEVELS OF TRYPTOPHAN AND URINARY 5HIAA

Subject	Tryptophan (mg./100 ml.)	5HIAA (mg./day)
12 normal subjects	1.06–1.28	*
17 patients without carcinoid	0.90–1.50	*
Patients with carcinoid†		
II	0.83, 0.81, 0.63	320–392
III	1.00, 0.74, 0.84	380–580
IV	0.70, 0.68, 0.65, 1.07	214–572
VII	0.67, 1.06	450–680
VIII	1.20, 1.14, 1.10, 1.19	157–192
X	0.45, 0.47, 0.65	380–630

* Usual range is 2–9 mg.
† The 5HIAA values represent the range obtained over a prolonged period of study.

Fasting plasma tryptophan levels were measured in twelve normal subjects (laboratory personnel), seventeen hospitalized patients who varied in nutritional state from emaciation to obesity, and in six patients with carcinoid. The measurements in the patients with carcinoid were made at a time when the daily tryptophan intake exceeded 1,000 mg./day and there was no diarrhea or change in weight. The results shown in Table III indicate that patients with carcinoid have significantly lower tryptophan levels. It is of interest that the patient (Case VIII) who had the lowest 5HIAA excretion also had the highest tryptophan levels, these being within normal limits. These results support the hypothesis of secondary tryptophan deficiency in this condition.

The daily urinary excretions of N′-methyl-nicotinamide (NMN) and total 5-hydroxyindole compounds in four patients are shown in Table

* The pool size of serotonin may be estimated by using the following equation:

$$\text{pool size (mg.)} = \frac{\text{production rate (mg.)}}{b}$$

where production rate is known (350 mg./day) and b, the rate constant of turnover, can be estimated, using the method of least squares, from the equation:

$$\text{specific activity} = ae^{-bt}$$

which represents the process of a simple turnover; a, in this equation equals pool size.

IV. It is apparent that the patients with the highest excretion of 5-hydroxyindoles had the lowest urinary NMN levels. Field and McDaniel [*16*] found NMN values in the order of 3.3 to 4.0 mg./day in normal subjects after ten to fourteen days on the restricted diet. (Table IV.) The excretions in Cases II and III are low. In Cases IV and VIII in which the 5-hydroxyindole excretions are not as great, the NMN excretions approach normal values.

TABLE IV
URINARY EXCRETION OF N′-METHYLNICOTINAMIDE (NMN) AND TOTAL 5-HYDROXYINDOLE (5-HI) COMPOUNDS

Day	Case II*		Case III*		Case IV†		Case VIII†	
	NMN (mg./day)	5-HI (mg./day)	NMN (mg./day)	5-HI (mg./day)	NMN (mg./day)	5-HI (mg./day)	NMN (mg./day)	5-HI (mg./day)
1	1.10	582	1.88	447	3.65	354	4.05	258
2	1.18	640	2.56	480	3.36	392	3.72	228
3	1.38	645	2.50	481	3.38	325	3.38	237
4	1.43	630	2.38	462	3.62	328	3.21	266
5	1.31	624	2.70	460	3.38	330	3.48	185

* Ad lib. food intake which provided greater than 1,000 mg. of tryptophan and 10 mg. of niacin per day.
† Special restricted diet containing approximately 800 mg. of tryptophan and 10 mg. of niacin per day.

Pharmacologic Studies. Reserpine: Shore et al. [*17,18*] have shown that the administration of reserpine to animals causes a release of serotonin from its body depots with a resultant outpouring of 5HIAA in the urine. The obvious implication in patients with carcinoid is to attempt to deplete tumor stores of serotonin by administration of reserpine. A patient (Case IV) was given a total of 140 mg. of reserpine orally over a period of twenty-five days; 10 mg./day being administered during the last six days. Although the drug was well tolerated, no change occurred in the daily excretion of 5HIAA. The resistance of the tumor to serotonin release by reserpine is consistent with its intestinal origin. Doses in the order of 3 mg./kgm. in rabbits are required to deplete the intestinal tract of serotonin.

It was shown by Haverback et al. [*19*] that the daily intramuscular administration of 1 mg. of reserpine in man for ten days reduced platelet serotonin by approximately 95 per cent. Comparable doses in rabbits likewise resulted in a decline in platelet and brain serotonin but the level in the intestine showed no significant change. It seemed of interest to study the effect of reserpine on the elevated platelet serotonin levels of patients with carcinoid. Measurements were made over a period of several weeks in two patients (Cases IV and VIII), with initial dosage of 1.0 mg./day, later decreased to 0.5 and 0.25 mg./day, respectively. The alterations in platelet serotonin are shown in Figure 2. With the 1.0 mg. dose, the platelet serotonin fell to negligible amounts within ten days. It would appear that approximately 1 mg. per day is needed to maintain platelet serotonin depletion. Lowering the dosage of reserpine caused a rise in each case. It is of interest that a similar amount of reserpine released serotonin totally from normal platelets which contain 0.3 to 0.6 μg. of serotonin per mg. of platelet protein as from carcinoid platelets, containing more than ten times this amount. *In vitro* studies by Shore et al. [*20*] show that the interaction of reserpine with serotonin is not of a competitive nature.

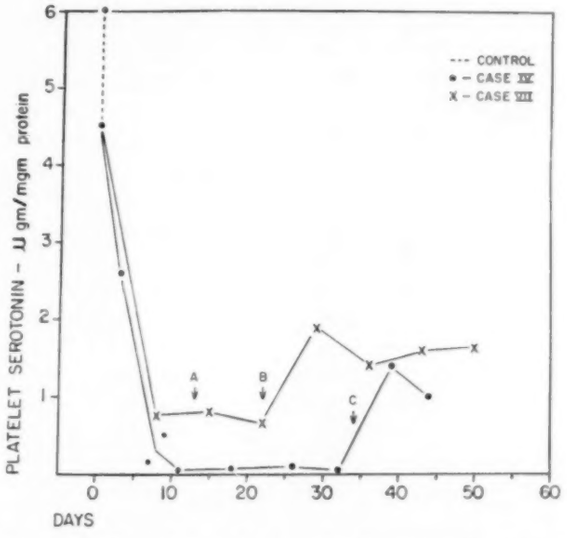

FIG. 2. Effect of reserpine on platelet serotonin. Initial dosage was 1.0 mg./day. In Case VII, A, indicates change in dosage to 0.5 mg./day and B, indicates change in dosage to 0.25 mg./day. At C, the dosage in Case IV was changed to 0.5 mg./day.

Serotonin "antagonists" and chlorpromazine: An agent which effectively blocks the physiologic effects of serotonin would be a useful addition to the management of these patients. As reported elsewhere [*21*], the hallucinogenic agent, lysergic acid diethylamide (LSD-25), a potent serotonin antagonist in smooth muscle, actually was found to induce symptoms of a type attributable to excess serotonin in two patients. There are now other reports of "serotonin-like" action of LSD *in vivo* [*22,23*]. Cerletti and Rothlin [*24*] found

that 2-brom-D-lysergic acid (BOL-148) strongly antagonized the actions of serotonin on smooth muscle without producing psychic disturbances. When BOL was administered orally for several days to three patients (Cases II, III and IV) in a maximal dose of 9.0 mg./day, it had no apparent effect on flushing or diarrhea.

The drug which has proved most useful is chlorpromazine. Its administration appears to decrease the frequency and severity of flushing reactions, is of value in allaying anxiety and has been very effective in controlling the nausea which afflicts some of these patients. Although it has been reported that chlorpromazine antagonizes certain effects of serotonin [*25*], it is possible that the efficacy of chlorpromazine in patients with carcinoid is unrelated to interaction with serotonin.

Psychologic Evaluation. Current speculation concerning a possible role of serotonin in brain function and the demonstration that elevated brain serotonin levels in animals [*15*] are associated with behavioral disturbances prompted a psychologic and psychiatric evaluation of five of these patients (Cases II, III, IV, VII and VIII). Although four of the five patients did demonstrate rather pronounced lability of mood, (becoming tearful rather easily) this slight alteration was not of such degree as to suggest any serious affective disorder and may have been no greater than one would find in any sample of patients with comparable serious organic disease. Results of the Wechsler Adult Intelligence Test and Minnesota Multiphasic Personality Inventory Test also did not reveal any characteristic personality changes associated with carcinoid.

These findings may be due to poor penetration of serotonin into the brain. In this regard, it has been shown that no increase in brain serotonin is observed following parenteral administration of large amounts of serotonin in animals [*26*]. The absence of serotonin in the spinal fluid of patients with carcinoid is again indicative of the inability of serotonin to penetrate into the central nervous system.

COMMENTS

On the basis of numerous case reports in the literature and the experience cited here it is apparent that metastatic carcinoid with associated "endocrine" manifestations is not a medical rarity. Increasing awareness and the availability of a simple chemical means of diagnosis are resulting in more frequent recognition of the disorder, sometimes in stages preceding development of the entire carcinoid syndrome. The diagnostic limit of urinary 5HIAA measurement remains to be ascertained, as indeed does the matter of whether or not all tumors which are termed carcinoid by the pathologist actually produce serotonin.

Although most clinical manifestations are explicable on the basis of the chemical abnormalities, the cardiac involvement cannot be explained as yet and has not been produced experimentally. As already mentioned, an attractive hypothesis is that the endocardial lesions result from direct chemical irritation and that destruction of free serotonin in the lungs accounts for the preponderance of right-sided involvement. Although a pulmonary arteriovenous difference of free serotonin in plasma may exist, it has not yet been demonstrated. As was indicated earlier, the greatest difficulty in attempting to relate the cardiac abnormalities to levels of free serotonin is that our knowledge of the actual status of serotonin in the circulating blood is inadequate. Studies on binding of serotonin to platelets indicate that this is a rather complex phenomenon and that the degree of binding can be modified by such factors as pH and temperature. Since current methods of isolation of platelet-free plasma do not take these factors into account, the significance of the serotonin measurements in plasma must be questioned. Experimentally, it is unlikely that attempts to produce cardiac lesions in animals with serotonin injections will be successful since the substance is rapidly metabolized. However, prolonged elevations of blood and tissue serotonin levels are obtainable by administration of the serotonin precursor, 5-hydroxytryptophan [*15*], and a study of this substance in rats is in progress.

Chemical and pharmacologic studies on these patients are of value not only for a better understanding of the disorder and development of therapy but also from the standpoint of research into fundamental aspects of serotonin action and metabolism. The demonstration of low urinary N′-methylnicotinamide and fasting plasma tryptophan levels in patients with advanced disease supports the previous concept that excess serotonin production results in a disorder of tryptophan metabolism. Calculations of serotonin turnover, pool size and tumor mass from data obtained using radioactive 5-hydroxytryptophan

afford another measure of the magnitude of the disorder. Since urinary 5HIAA is a sensitive index of the mass of functioning tumor, its measurement will be useful in following the course of the disease and in evaluating the effectiveness of therapy designed to eradicate the tumor or to prevent formation of serotonin. Finally, the possibility of blocking serotonin effects in these patients by various drugs requires further investigation. As yet no effective pharmacologic antagonist of serotonin in these patients has been found, with the possible exception of chlorpromazine. The value of these patients in screening for drugs with antiserotonin activity is apparent.

Studies in these patients have made it possible to solve several problems concerning serotonin. The most outstanding of these are the demonstration that tryptophan is the dietary precursor of serotonin [*1*] and the recent isolation by Dalgleish [*27*] of 5-hydroxytryptophan from the urine of a patient with carcinoid with renal metastases. The latter finding represents the first direct demonstration of this amino acid in mammals and provides the final evidence needed to establish 5-hydroxytryptophan as the intermediate between tryptophan and serotonin.

SUMMARY

1. Studies on nineteen patients with metastatic carcinoid are presented.

2. Additional case reports illustrate the variability of clinical manifestations associated with carcinoid. It is now clear that some patients with extensive metastatic carcinoid do not show all, or even the predominant manifestations of the "carcinoid syndrome."

3. Chemical analyses confirm previous findings of excess serotonin production in this disorder. Also, the findings of low fasting plasma tryptophan and urinary N′-methylnicotinamide in some patients substantiate previous suggestions of a disorder in tryptophan metabolism in this condition.

4. A tracer study, in one patient, with the serotonin precursor, 5-hydroxytryptophan, enabled calculation of the tumor pool of serotonin (2,800 mg.), its turnover rate (one-half life of five and one-half days), and the tumor mass (between 1 and 3 kg.).

5. Increases in the urinary excretion of 5-hydroxyindoleacetic acid (5HIAA) in a patient during severe flushing episodes suggests that the flushes are mediated by increased serotonin release even though no concomitant rise in blood serotonin could be measured.

6. Cardiac catheterization studies revealed no measurable differences in the serotonin content of mixed venous and arterial blood which, if present, might account for predominant right-heart involvement. It is suggested that if a pulmonary arteriovenous serotonin difference does exist, it is in that portion which is free in the plasma. Difficulties in determining plasma serotonin are discussed.

7. The absence of serotonin in cerebrospinal fluid and the essentially negative results of psychologic evaluation in five patients probably indicate that serotonin does not penetrate readily into the central nervous system.

8. With the possible exception of chlorpromazine, drug therapy has proved ineffective.

Acknowledgments: The authors sincerely appreciate the cooperation of the many physicians who referred material for study. We wish to acknowledge particularly the collaboration in some of these studies of Dr. J. R. Sommer, Garfield Memorial Hospital, Washington, D. C., and Dr. T. P. Waalkes and Dr. J. D. Davidson, National Heart Institute, Bethesda, Maryland, We are indebted to Dr. C. Kornetsky and Dr. E. V. Evarts, National Institute of Mental Health, Bethesda, Maryland, for the psychologic evaluations. The technical assistance of Miss Colette A. Robillard is appreciated.

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Determination of 5-Hydroxytryptamine, 5-Hydroxyindole Acetic Acid and Histamine in Thirty-three Cases of Carcinoid Tumor (Argentaffinoma)*

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IT now seems to be generally accepted that metastatic malignant abdominal carcinoid (argentaffinoma) causes a syndrome of which the predominant symptoms are flushing [*1a*], right-sided valvular lesions of the heart and increased peristaltic activity. It was suggested [*1b,2*] that these symptoms were due to secretion of 5-hydroxytryptamine (enteramine, serotonin) by the carcinoid tumor. This hypothesis was supported by the finding that large amounts of 5-hydroxytryptamine (5HT) could be extracted from a carcinoid tumor (2.5 mg. per gm. tissue) [*3a,b*]. The explanation of the symptoms put forward by Waldenström was further confirmed by Pernow and Waldenström [*4*] who reported increased amounts of 5HT in the blood serum and urine in two cases of metastasizing carcinoid (carcinoidosis). An extremely high urinary excretion of 5-hydroxyindole acetic acid (5HIAA) has been found in such cases, another indication of the increased formation of 5HT in this disease [*5–8*].

The finding of an abnormally high concentration of 5HT in the blood and urine in carcinoidosis has subsequently been confirmed by several investigators [*9–15*]. The amounts reported in blood serum have varied between 0.2 and 6.5 μg. per ml. whereas normal values are 0.03 to 0.2 μg. per ml. [*9,14,16,17*]. Pernow and Waldenström [*18*] and Sjoerdsma et al. [*15*] found that the 5HT content of the blood in patients with carcinoid tumor was bound to the platelets and that practically no 5HT activity was present in platelet-free plasma, as in normal persons. Snow et al. [*9*], however, reported considerable amounts of 5HT in platelet-poor plasma in two cases. The urinary excretion of 5HT in patients with carcinoid has been reported to be 0.4 to 20 μg. per ml. [*9,10*], whereas 0.01 to 0.7 μg. per ml. can be extracted from normal urine [*10,15,19*].

The normal twenty-four-hour urinary excretion of 5HIAA has been reported to be 3 to 6 mg. [*20*], 2 to 10 mg. [*21*] and 2 to 8 mg. [*6*]. In subjects with carcinoid this excretion is greatly increased, to amounts between 60 to 2,000 mg. per twenty-four hours. The daily 5HIAA excretion, which normally is very constant [*21*], is subject to marked daily variation in carcinoidosis [*7,9*].

In this paper twenty-two cases of metastatic abdominal carcinoid tumor are presented. The diagnosis was established by clinical, biologic, chemical and microscopic observations. Urine specimens from eleven patients, after probably complete resection of carcinoid tumor, have also been examined. The results of repeated analyses of 5HT and 5HIAA in the blood and urine of several patients are recorded. In nine cases the urinary excretion of histamine also has been studied. In a preliminary study this was shown to be increased in some but not in all cases [*18*].

METHODS

Preparation of 5HT Extracts. The blood serum was mixed as soon as possible with 20 volumes of acetone and thereafter kept in the cold (+4°C.) overnight. After centrifugation the acetone was evaporated *in vacuo* from the clear centrifugate. The residue was used without delay for assay.

The method employed to prepare extracts from

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urine depended on its content of 5HT. Twenty volumes of acetone was always immediately added to the urine. It was then treated as described for serum. If 0.05 ml. of urine did not give any measurable effect on the intestine in the assay, it was further purified according to a method modified after Bumpus and Page [*22*]. The urine was acidified to pH 5 with HCl and concentrated *in vacuo* at 30°C. to $\frac{1}{10}$ of the original volume. It was thereafter incubated with urease (5 gm. per 100 ml. original urine) for three hours at 45°C. Methanol was added to 30 volumes per cent and an additional 20 volumes of acetone, with stirring. After centrifugation the acetone was evaporated, the residue mixed with aluminum oxide (2 gm. per 10 ml. of extract) and filtered. The filtrate was then used for assay.

Extraction of Histamine from Urine. The histamine was adsorbed on an ion exchange column (Amberlite IRC-50) according to a method outlined by Bergström and Hansson [*23*], modified for blood and urine by Dunér and Pernow [*24*].

Extracts of tissue have been made, in part by the method described by Feldberg and Toh [*25*]. After removal at operation the tissue was placed in acetone. It was then finely minced with a pair of scissors, ground with sand in acetone, and kept in the acetone overnight at +4°C. After filtration the solid residue was again ground up with small amounts of fresh acetone. To the combined filtrates was added 2 to 5 ml. of water and the acetone evaporated *in vacuo* at room temperature. The residue was then immediately used for assay.

Biologic Assay. The extracts of blood serum, urine and tissue were assayed for their 5HT activity using the isolated rat colon or uterus. The bath volume was 3 ml., as bath fluid a Tyrode solution was used, with reduced Ca^{++} content. The fluid was aerated with pure oxygen and kept at a temperature of 28°C. To the bath fluid was added atropine sulphate (1 mg./L.). Rat colon was used for routine work since it seems to be a better test object for urine analyses. The uterus is more sensitive for contaminating substances in the urine. The histamine activity of the extracts was assayed on the isolated guinea pig ileum in Tyrode's solution to which dihydroergotamine (5 μg. per ml. bath fluid for ten minutes) usually was added in order to abolish the effect of 5HT.

Determination of the 5HIAA content of the urine was carried out by the colorimetric method of Udenfriend, Titus and Weissbach [*27*] using 1-nitroso-2-naphthol as reagent.

As a rapid test for identification of large amounts of 5HIAA the urine was mixed with equal amounts of Ehrlich's reagent [*7*]. A dark blue color develops in 5 to 8 hours. The reaction is positive if the urine content of 5HIAA is greater than 0.03 mg. per ml.

Paper chromatography of 5HT and 5HIAA was carried out with butanol/acetic acid/water (40:10:50) as solvent. The papers were developed with Ehrlich's reagent. For the identification of 5HIAA the urine was chromatographed without any treatment beforehand, whereas 5HT was usually detectable only after concentration of urine and precipitation of salts and proteins with acetone. Before chromatography the serum was mixed with 20 volumes of acetone, centrifuged and concentrated *in vacuo*. The chromatographic method was used only for qualitative identification of the substances.

The 5HT activity was assayed against serotonin creatinine sulphate (Abbott Laboratories). The 5HIAA was synthesized and kindly supplied by Dr. Asero, Farmitalia, Milan, Italy. The figures for 5HT and histamine given in this paper refer to the bases.

The Specificity of the 5HT Determination. The evidence that the biologically active principle was 5HT is as follows:

1. *Solubility:* The substance was soluble in 95 per cent acetone and alcohol, but was insoluble in ether. The effect could therefore not be due to any biologically active polypeptide such as posterior pituitary hormones, bradykinin, substance P, kallidin, substance U (Beraldo [*26*] or the substance recently found in urine by Gomes [*27*]). It could also not be due to adenosine compounds or potassium salts, which are practically insoluble in 95 per cent acetone.

2. *Stability:* The substance is stable when boiled in neutral solution but is unstable in N HCl and N NaOH, which is in conformity with the results by Amin, Crawford and Gaddum [*28*].

3. *Enzymatic inactivation:* The active principle is not inactivated by trypsin or chymotrypsin, which excludes the presence of active polypeptides. It is also not inactivated by purified histaminase.

4. *Biologic action:* The substance stimulates the isolated guinea pig ileum, rat colon and rat uterus. This effect is not blocked by atropine or antihistaminics in specific doses. It is blocked by tryptamine, dihydroergotamine or large doses of 5HT, drugs which are known to have a specific action on the tryptamine receptors [*29*]. The rat colon and uterus used for assay are practically insensitive to histamine. Acetylcholine causes a contraction but atropine was routinely used to prevent errors due to this drug. It is not likely that adrenaline or noradrenaline were present in the urine in amounts sufficient to diminish the stimulating effect of 5HT.

5. *Paper chromatography:* Extracts of blood serum and urine from the patients with carcinoid gave, after developing with Ehrlich's reagent, a positive spot with the same RF value as 5-hydroxytryptamine creatinine sulphate. Biologic assay of strips of corresponding papers also indicated that this spot really represented the 5HT activity of the extracts.

The Presence of Histamine in the extracts was demonstrated by the following biologic and chemical methods:

1. The extracts had a stimulating effect on the isolated guinea pig ileum, but had practically no effect

TABLE 1

RESULTS OF 5-HYDROXYTRYPTAMINE (5HT) AND 5-HYDROXYINDOLE ACETIC ACID (5HIAA) ANALYSES IN NON-OPERATED CASES AND IN OPERATED CASES IN WHICH THE CARCINOID TUMOR WAS NOT COMPLETELY RESECTABLE

Case	Flush	5-Hydroxytryptamine		5HIAA (urine) (mg./24 hr.) (normal: 2 to 10)	Tissue 5HT* (μg./gm.)	Diagnosis†
		Blood Serum (μg./ml.) (normal: 0.03 to 0.2)	Urine (μg./24 hr.) (normal: <200)			
With Increased Amounts of 5HT and/or 5HIAA						
1. S. H.	+	5.2	....	.....	70 (L)	CL
		0.8	....	.....	.....	.....
		1.2	....	.....	.....	.....
2. E. P.	+	4.3	....	145	.....	CL
3. H. B.	+	0.9	370	.....	23.7 (L)	CLM
		0.7	530	50–200	53.5 (M)	.....
4. V. S.	+	0.25	....	.....	92 (L)	CLM
		0.4	....	50	25 (M)	.....
		1.1	....	.....	18 (M)	.....
5. A. J.	+	1.4	630	.....	.....	CL
6. V. M.	+	0.45	....	25–200	.....	CLM
		0.8	....	.....	.....	.....
7. E. H.	+	0.9	....	100	.....	CL
				45	.....	.....
8. J. J.‡	+	0.25	....	45	432 (T)	C in teratoma
		0.45	350	16	.....	.....
		0.3	....	22	.....	.....
9. J. B.	+	0.05	100	6	.....	C
				12	.....	.....
				20	.....	.....
				16	.....	.....
10. R. E.	+	0.3	690	150	.....	CL
			1320	.....	.....	.....
11. L. C.	+	....	....	210	.....	CL
12. V. W.	+	....	720	452	.....	CL
13. M. N.	+	0	100	50	.....	CL
14. M. C.	+	....	300	40	.....	CL
15. H. S.	0	0.15	410	110	.....	CLM
16. T. N.	+	....	220	120	.....	CL
				170	.....	.....
				230	.....	.....
17. O. P.	0	....	....	19	.....	CM
18. E. H.	+	....	....	16	.....	C

TABLE I (*Continued*)

RESULTS OF 5-HYDROXYTRYPTAMINE (5HT) AND 5-HYDROXYINDOLE ACETIC ACID (5HIAA) ANALYSES IN NON-OPERATED CASES AND IN OPERATED CASES IN WHICH THE CARCINOID TUMOR WAS NOT COMPLETELY RESECTABLE

Case	Flush	5-Hydroxytryptamine		5HIAA (urine) (mg./24 hr.) (normal: 2 to 10)	Tissue 5HT* (μg./gm.)	Diagnosis†
		Blood Serum (μg./ml.) (normal: 0.03 to 0.2)	Urine (μg./24 hr.) (normal: <200)			
With Increased Amounts of 5HT and/or 5HIAA						
19. S.	0	....	620	46	.....	CLM
				48	.....	.....
20. A. L.	?	....	570	21	205 (M)	CM
				24	.....	.....
21. O. O.	?	....	....	14	.....	.....
With Normal Amounts of 5HT and 5HIAA						
22. I. L.	0	....	100	4	15 (T)	CM
R. L. E.	+	0.3	4620	105	.....	Bone metastases; primary?
		0.3	4205	90	.....	Histology uncertain
			2700	140	.....	.....
			3210	.....	.....	.....

* L = Liver metastases, T = Primary tumor, M = Mesenteric node metastases

† C = Carcinoid, CL = Carcinoid metastasizing to liver, CM = Carcinoid metastasizing to mesenteric nodes.

‡ After complete resection of an ovarial teratoma the flushes disappeared and the excretion of 5HIAA became normal. This case will be reported in detail elsewhere.

on the rat colon or uterus. They had a marked depressant action on the blood pressure of the cat. The effects on the guinea pig gut and the blood pressure of the cat were completely inhibited by antihistaminics.

2. The activity of the extracts was completely destroyed by highly purified histaminase preparations.

CASES

The case material consisted of thirty-three patients with abdominal carcinoid tumour (argentaffinoma), the diagnosis in each instance being verified by histologic examination; and one case (R. L. E.) of "carcinoma" of unknown type, previously described by Waldenström, Pernow and Silwer [*30*]. Fourteen patients (Cases 1, 2, 3, 6, 8, 16, 17, 18, 21, 26, 27, 28, 29 and 31) have been observed and followed up by us. Cases 1, 2, 3 and 6 have been described in detail by Waldenström and Ljungberg [*31*]. Further clinical studies on these cases will be published by Thorson. Some of the 5HIAA determinations in these patients were made by A. Hanson, for which assistance we want to express our thanks. These figures are included in Table I. The other patients have been examined and diagnosed in different Swedish hospitals. A detailed study of Case 4 has been published by Molander [*32*]. In these patients we have performed only the biologic and chemical analyses.

Since our intention was to study the significance of 5HT and 5HIAA analyses, the material has been divided into two parts: (1) Patients who were examined before operation or in whom complete resection of the tumor was not possible (Table I) and (2) patients in whom resection was probably complete. (Table II.) The chief symptoms in most cases in group I have been attacks of flushing, borborygmus, diarrhea, asthma and, in some cases, right-sided valvular disease of the heart. In six patients (Cases 5, 6, 7, 8, 12 and 14) operation had been performed after the biologic and chemical analyses had shown the presence of 5HT-producing tumor tissue. The other patients had

TABLE II

RESULTS OF 5HT AND 5HIAA ANALYSES IN CASES IN WHICH THE CARCINOID TUMOR PROBABLY WAS COMPLETELY RESECTED

Case	Flush	5-Hydroxytryptamine		5HIAA (urine) (mg./24 hr.)	Tissue (primary tumor) (μg./gm.)	Location of Carcinoid Tumor
		Blood serum (μg./ml.)	urine (μg./24 hr.)			
23. M. T.	0	.....	<150	3	65	Colon, metastases to umbilicus
24. A. R.	0	<0.05	<150	5	..	Rectum
25. B. S.	0	.....	<100	3	..	Appendix
26. S. S.	0	.....	.....	3.7	..	Cecum
27. S. K.	0	.....	.....	20	..	Ileum
28. H.	0	.....	.....	18	..	Appendix
29. G. P.	0	.....	....	12	..	Ileum
30. A. P.	0	.....	.....	15	..	Ileum
31. H. Ä.	0	.....	<100	4	..	Appendix
				5	..	.....
32. E. E.	0	.....	.....	13	..	Ileum
33. E. G.	0	.....	.....	10	..	Ileum

been operated upon with the suspicion of conditions such as cancer coli and appendicitis, or the carcinoid tumor was accidentally found at laparotomy undertaken for other reasons. Patient R. L. E. has a malignant tumour of unknown primary site, with metastases to the lungs and the skeleton. Biopsy of a skeletal metastasis revealed a carcinoma of unknown type, possibly a carcinoid.

Many cases were followed with repeated biologic and chemical assay over a period of up to two years.

Another series (Table II) comprises cases in which the carcinoid tumor was detected at operation and completely resected. These patients had no clinical symptoms typical of the carcinoid syndrome before or after the operation. No metastases were detected at laparotomy.

RESULTS

The biologic and chemical analyses in the non-operated and not completely resected carcinoid cases (Table I and Fig. 1) gave the following results:

5HT. The 5HT assay was made in blood serum in thirteen cases and in urine in fourteen cases. Large amounts were found in the blood in nine patients, in the urine in ten patients. Normal values were obtained in the remaining cases (Cases 9, 13, 16 and 22). The figures for 5HT in the blood serum varied between 0.05 and 5.2 μg. per ml. and in the urine between 0.1 and 4.2 μg. per ml. (0.1 to 4.6 mg. per twenty-four hours).

Extracts of carcinoid tumor tissue, taken at operation in five cases, were also assayed for 5HT. The tissue consisted of the primary tumor and metastases to the liver and the lymphatic glands. The 5HT content of these tissue extracts varied from eighteen to 432 μg. per gm. wet weight, the highest activity being found in the primary tumor of the patient in Case 8.

5HIAA. The urinary excretion of 5HIAA was repeatedly studied in twenty-one patients. High values were obtained in all cases except one (Case 22). The figures varied between 14 and 452 mg. per twenty-four hours (normal 2 to 10).

Histamine. The excretion of histamine in the urine varied greatly in the nine tumor cases in which this assay was performed. (Table III.) In seven cases the histamine excretion was greater than normal. The highest excretion of histamine was found in patient R. L. E. with a twenty-four hour value of 4.6 to 6.8 mg. (For details see Waldenström, Pernow and Silwer [*30*].) In Case 22, in which a histologically verified metastasizing carcinoid was found (without, however, any general symptoms), the urinary excretion of histamine was probably significantly increased (54 μg. per twenty-four hours). The 5HT and 5HIAA figures were quite normal in this case. In case R. L. E. the histamine content of the blood serum also was determined. This was found to be 0.3 μg. per ml. (normal

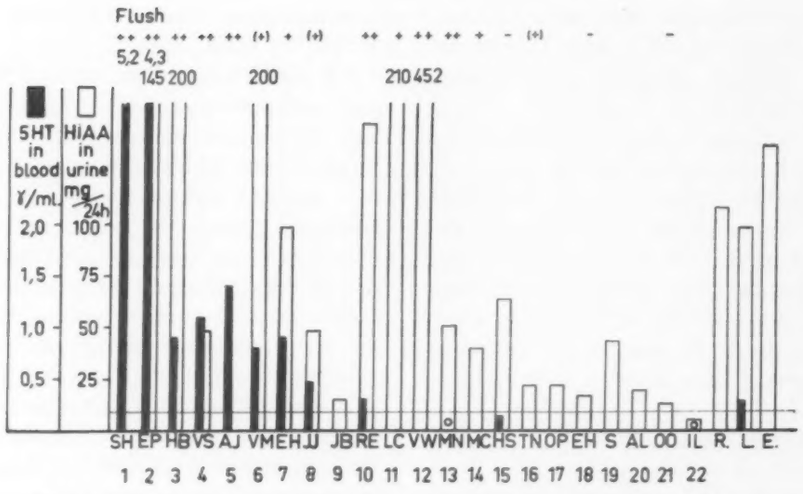
Flush
5,2 4,3
145 200
200
210 452
5HT in blood γ/mL
HIAA in urine mg/24h
2,0
1,5
1,0
0,5
100
75
50
25
SH EP HB VS AJ VM EH JJ JB RE LC VW MN MC HS TN OP EH S AL OO IL R. L E.
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

FIG. 1. Data in non-operated and not completely resected carcinoid cases.

<0.03 μg. per ml.). Since these results were reported [4], Snow et al. [9] published histamine determinations in two cases of carcinoids. The histamine figures found were quite normal.

The results of the 5HT and 5HIAA analyses in the patients with carcinoid who did not show any signs of carcinoidosis are collected in Table II and Figure 2. The 5HT content of the blood serum and urine was normal. The urinary excretion of 5HIAA varied between 3 and 20 mg. per twenty-four hours.

TABLE III
URINARY EXCRETION OF HISTAMINE, 5HT AND 5HIAA IN CASES OF CARCINOID TUMOR

Case	Histamine (μg. per 24 hr. normal: 6 to 19)	5HT (μg. per 24 hr. normal: <200)	5HIAA (mg. per 24 hr. normal: 2 to 10)
Not explored or tumor not completely excised			
8. J. J.	27	125	22
	38	.....	45
9. J. B.	40	.....	19
	8	.....	6
10. R. E.	48	1320	150
12. V. W.	125	790	452
16. T. N.	900	220	170
	2600	.....	230
19. S.	15	620	46
	12	.....	48
20. A. L.	15	570	21
	22	.....	24
22. J. L.	54	<100	4
R. L. E.	4600	4625	105
	6800	4205	90
	4700	2700	...
Tumor probably completely resected			
26. S. S.	4	.....	4

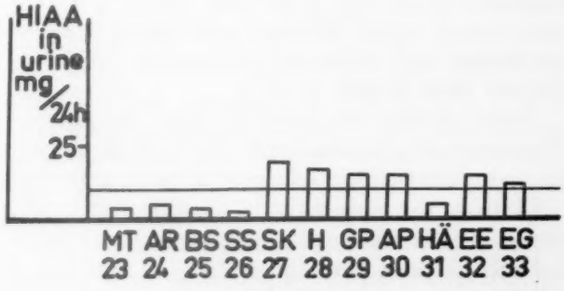

FIG. 2.

COMMENTS

The diagnostic importance of 5HT determinations in blood and urine, and of its metabolite, 5HIAA, in urine, in cases with carcinoid tumor is quite evident from the results presented herein. This applies both to establishing the diagnosis and to evaluation of the extent of operative extirpation or of metastatic spread. In Cases 5, 6, 7, 8, 12 and 14 the biologic and chemical investigations established the diagnosis, which was thereafter verified at laparotomy and by microscopic studies. In Cases 9, 14, 15 and 16 repeated postoperative analyses showed that spread of the tumor had occurred, which was confirmed in the three last named cases by re-exploration.

A distinctly elevated 5HT level in blood serum and urine, and of 5HIAA in urine, was demonstrated in those cases in which the flushing,

typical of carcinoid, was the predominant symptom. With regard to 5HT, case 13 was an exception, the patient showing pronounced flushing without increase in serum 5HT, and a greatly elevated urinary output of 5HIAA. In this instance there may have been a technical error in the extraction procedure or incorrect preparation of the specimen before transport. We were unable in this series to establish any definite correlation between the severity of flushing and the 5HT content of blood or urine, since we had no opportunity to observe all the cases ourselves. However, Cases 1 and 2 showed unusually marked flushing and the highest 5HT content hitherto found in the blood.

In the verified cases of carcinoid without flush symptoms, elevated 5HT and 5HIAA values were observed in only one patient (Case 15), in whom carcinoid of the appendix was discovered at operation for appendicitis. The patient was readmitted some years later for investigation of anemia and fatigue. He did not complain of any flush symptoms, nor were any observed at the hospital. Since the 5HT and 5HIAA values were clearly abnormal he was re-explored. Liver metastases and numerous mesenteric node metastases were found.

There should be no doubt that the general symptoms which dominate the clinical picture in abdominal carcinoid are due to secretion of 5HT from the tumor tissue, as reflected in the elevated 5HT content of the blood serum. Identical effects have been produced by infusion of 5HT into human and laboratory animals. The flush symptom was experimentally duplicated by Roddie et al. [*33*], who showed that infusion of 5HT into the human brachial artery produced a deep red flush in the injected arm, which gradually became increasingly cyanotic. Concomitantly there was an increase in volume of the forearm and hand, and reduced dissipation of heat. These phenomena were due to pronounced contraction of arteries and arterioles and dilatation of capillaries and venules. This symptom has also been observed after intravenous injection of 5HT [*34*]. Reid and Rand [*35*] studied in detail the action of 5HT on the pulmonary circulation and recorded a greatly elevated pressure in the right ventricle and pulmonary artery, as well as bronchoconstriction. The marked stimulating effect of 5HT on smooth muscle, notably in the alimentary tract, has been studied most extensively by Erspamer [*36*]. Borborygmus and abdominal pains have also been observed after intravenous administration of 5HT in man [*37*].

All patients in this series who had flush symptoms and presented high 5HT and 5HIAA levels had carcinoid tumors with liver metastases (except Case 8). It seems probable, therefore, that general symptoms usually do not appear until the tumor has metastasized to the liver. The liver metastases are therefore likely to constitute the principal 5HT-producing tissue. In Cases 1 and 2 flushing continued after the primary tumor had been excised. The only patient with carcinoid (Case 22) in whom preoperative assays of 5HT and 5HIAA showed normal values had a tumor of the small intestine with mesenteric node metastases but no demonstrable liver metastases. This patient had presented no flush symptoms. Hence it cannot be claimed that normal 5HT or 5HIAA values prove the absence of lymphatic metastases but probably do of large hepatic metastases.

Waldenström and Ljungberg [*31*] discussed the possibility of distinguishing different types of carcinoid tumors either by histologic differentiation or by chemicobiologic studies. Case 22 may perhaps serve to illustrate this problem by representing, in the endocrine sense, a more benign type than the others in this series. The patient in question underwent operation for cholecystitis, and inspection of the abdomen disclosed an intestinal tumor which had the typical microscopic structure of a carcinoid. Mesenteric node metastases were discovered at a second operation. This patient showed none of the symptoms characteristic of metastasizing carcinoid. The primary tumor contained 15 μg. 5HT per gm. of tissue, a value normal for intestinal tissue. The possibility nevertheless exists that if metastatic spread to the liver continues this tumor may produce the complete symptomatology of carcinoidosis later on. The urine content of 5HIAA was normal.

The value of repeated determinations of urinary 5HIAA in suspected cases of carcinoid was illustrated by Hanson and Serin [*7*]. We would emphasize this, in particular for postoperative follow-up. In two of our patients (Cases 9 and 18) the observed 5HIAA values were only slightly above the normal, and in some cases abnormal values were not obtained until repeated examinations had been made. This is well illustrated by Case 9.

It is noteworthy that so often, when the chemical findings did not indicate the presence

of metastases, the values for 5HIAA nevertheless were slightly above the normal (Cases 27, 28, 29, 30, 32). Our data are not yet sufficient for a discussion of this finding. Perhaps there are cases with hypertrophy of the yellow cells without discrete tumors. Further anatomic and clinical results will be needed to clarify this point.

The elevation of the 5HT content of the blood runs parallel with the increased urinary output of 5HIAA. Although from a physiologic point of view greater interest attaches to a study of the biologically active constituent (5HT), determinations of 5HIAA are definitely to be recommended as a routine procedure when there is suspicion of carcinoid or in postoperative follow-up. This latter method of determination is simpler and requires less laboratory equipment; 5HIAA is considerably more stable than 5HT and hence the values obtained are more reliable. The moderate increase in blood 5HT in these cases doubtless reflects substantial secretion of 5HT from the tumor tissue. The greater part of this substance is taken up by the tissue [*38*] and the platelets [*39*]. It is known that 5HT is broken down by aminoxidase [*40*]. This portion of the secreted 5HT can also be determined in the form of 5HIAA in the urine. It has been shown, however, that there are also other metabolites of 5HT [*8,22*].

The fact that both histamine and 5HT may be found in increased amounts in the blood and urine in these cases suggests some relationship between these substances in the body. Other observations also speak in favor of this suggestion. It has been pointed out by Douglas et al. [*41*] that the distribution of 5HT in the mucosa of the stomach is very similar to that of histamine. Recently, the presence of both histamine and 5HT has been demonstrated in the mast cells (Benditt et al. [*42*]). We have studied the urinary excretion of histamine and 5HIAA in one case of urticaria pigmentosa. The histamine value was very high (189 μg./24 hr.) whereas the 5HIAA excretion was normal (6.2 mg./24 hr.) [*43*].

Nothing is known about the mechanism of release of histamine in these patients. It might be assumed that the tumor cells produce both 5HT and histamine.

Another explanation might be that increased formation of 5HT in the tumor cells leads to secondary release of histamine. This would be in conformity with the results of Feldberg and Smith [*44*] who showed that 5HT can release histamine from living cells.

SUMMARY

Determinations of 5-hydroxytryptamine (5HT) in blood serum and urine and of 5-hydroxyindole acetic acid (5HIAA) in urine were made in thirty-three cases of abdominal carcinoid tumor (argentaffinoma).

The cases were divided into two groups: (1) Twenty-two cases which were examined before operation or in which the tumor was not completely resected. The 5HT analyses showed increased values in blood and/or urine in seventeen of eighteen cases, with figures ranging from 0.15 to 5.2 μg. per ml. blood serum and 0.1 to 4.2 μg. per ml. urine. Abnormally high 5HIAA values were obtained in nineteen of twenty cases (12 to 452 mg. per 24 hr.). (2) Eleven cases in which the tumor had been removed, probably *in toto*. In this group the 5HT and 5HIAA figures were normal or slightly increased.

In eight cases in group 1, and in one "cancer" patient (R. L. E.), the urinary excretion of histamine also was studied. In seven cases an increased excretion was found, with figures ranging from 27 (borderline value) to 6800 μg. per twenty-four hours. There was striking variation in these values. The significance of the correlation between increased 5HT metabolism and the general symptoms of carcinoidosis is discussed, together with the significance of the increased urinary excretion of histamine.

Of unusual interest is Case 8 in this series, a patient who showed high values for HIAA in urine, chronic flushing of the face, signs of pulmonary heart disease and "pellagra." She was found to have a non-malignant ovarian teratoma with argentaffine cells in large numbers. After operation all symptoms (except the cardiac) disappeared and the excretion of HIAA has remained normal.

Acknowledgments: We want to thank a great number of colleagues from this country and from abroad through whose interest in this investigation valuable case material was afforded us for study.

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Lactescence of Serum Following Episodes of Acute Alcoholism and Its Probable Relationship to Acute Pancreatitis*

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HIGH concentrations of triglyceride (neutral fat) in particulate form impart a characteristic milky turbidity to the blood serum known as lactescence [*1*], a condition that has been observed in patients with diabetic acidosis, nephrosis, familial hyperlipemia or acute pancreatitis. The accumulation of lipids in the serum appears to be related to the defect in carbohydrate metabolism in patients with diabetic acidosis [*2*], and to the decrease in serum albumin in patients with nephrosis [*3*], but its pathogenesis in both familial hyperlipemia and in pancreatitis is obscure.†

Lactescence of serum occurs in only a small proportion of patients with acute pancreatitis. In some patients, both the lactescence and the pancreatitis appear to be manifestations of an underlying familial hyperlipemia [*4*], while in other patients the lactescence appears to be directly related to the pancreatitis itself [*5–7*]. Although mild glycosuria is an occasional complication, the hyperlipemia is rarely if ever due to diabetic acidosis. In the group with familial hyperlipemia, the pancreatitis is usually of the relapsing type and has its onset in childhood or early adult life. Characteristically, the hyperlipemia is sustained, except for brief periods following an attack, and may be accompanied by xanthomatosis and lipemia retinalis. Occasionally there is a family history of recurrent abdominal pain or xanthomatosis, and blood studies may confirm the familial nature of the hyperlipemia. Following stringent restriction of dietary fat, the serum clears, xanthomas vanish, and attacks of pancreatitis cease [*4*]. In the nonfamilial group, the onset of pancreatitis is in the fourth decade or later, relapses are an inconstant finding, and lactescence of serum is a transient phenomenon which may last from a few hours to several days. A similar type of transient hyperlipemia has been observed in dogs with experimentally induced hemorrhagic pancreatitis [*8*].

The purpose of this paper is to report the occurrence of serum lactescence following bouts of acute alcoholism and to indicate the probable relationship of this type of hyperlipemia to acute pancreatitis. The five patients to be described were all middle-aged chronic alcoholic subjects with abdominal pain who exhibited marked but transient lactescence of the serum. In none was there evidence of familial hyperlipemia. The diagnosis of acute pancreatitis was established by laparatomy performed in one and was considered highly probable on clinical grounds in the others. The serum lipid values are shown in Table 1. The lipids determined were total fatty acids, total and free cholesterol, and lipid phosphorus. Triglyceride (neutral fat) was calculated by difference. The methods used have been previously described [*9*].

CASE REPORTS

CASE 1. E. S. (B32010), a thirty-eight year-old white man, was admitted to the hospital on November 28, 1945, with acute delirium tremens and burning epigastric pain. He gave a history of chronic alcoholism and an alcoholic bout just prior to admission. On examination the temperature was 38°C. There was considerable epigastric tenderness and spasm. The liver was palpable 4 fingerbreadths below the right costal margin. The serum was markedly lactescent. On admission the leukocyte count was 7,300 per cu.

† At the Third International Conference on Biochemical Problems of Lipids, Brussels, July 1956, Havel reported evidence suggesting that familial hyperlipemia is caused by a deficiency of lipoprotein lipase.

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TABLE I

SERUM LIPIDS IN PATIENTS WITH LACTESCENCE OF SERUM FOLLOWING ACUTE ALCOHOLISM

Case No.	Age (yr.)	Sex	Date	Total Fatty Acids (mEq./L.)	Cholesterol			Lipid Phosphorus (mg. %)	Triglyceride Fatty Acids (mEq./L.)
					Total (mg. %)	Free (mg. %)	Free (%) Total		
I (B32010)	38	M	11/28/45	141.0	713	518	73	54.8	104.0
			11/29/45	53.4	598	464	78	48.4	22.5
			12/3/45	30.2	579	301	52	29.7	5.2
			12/6/45	20.9	432	161	37	18.0	6.8
			12/13/45	12.7	267	80	30	11.4	4.0
II (A84592)	38	M	7/7/51 preoperatively	82.8	694	262	38	....	.....
			2 hr. postoperatively	64.6	....	...	..	....	.....
			8 hr. postoperatively	22.3	498	136	33	....	.....
			9/14/52 (9:30 P.M.)	172.5	....	....	..	....	.....
			9/15/52 (midnight)	167.5	1105	460	42	52.6	100.3
			2:00 A.M.	151.0	....	...	..	....	.....
			7:00 A.M.	84.4	814	337	41	35.8	51.3
			9/16/52	26.4	562	209	37	22.9	3.1
			9/17/52	21.7	428	...	..	....	.....
			9/19/52	20.1	397	...	..	....	.....
			9/23/52	23.4	404	...	..	....	.....
			10/26/52	16.7	202	63	31	14.6	4.6
III (37-62-54)	42	M	8/25/52	82.0	304	172	57	25.4	64.0
			8/28/52	13.8	120	72	60	8.7	7.6
			9/2/52	11.2	96	43	45	6.3	6.1
IV (58575)	43	M	2/5/52	120.3	505	...	..	....	.....
			2/6/52	32.8	397	...	..	....	.....
			3/5/52	21.6	319	74	23	12.7	7.8
			10/21/55 (8:00 P.M.)	52.8	341	...	..	18.8	37.8
			10/24/55	16.7	222	95	43	11.9	6.5
			11/2/55	17.0	213	73	34	11.0	8.0
V (93704)	40	M	8/20/53	64.2	457	286	62	24.3	45.7
Normal values [9]				12.3	194	54	28	9.2	3.1

mm., fasting blood sugar, 83 mg. per cent; the icterus index, 7; urine bile, 1 plus; urine urobilinogen, 2 plus. Two days later total serum proteins were 5.8 gm. per cent, albumin, 3.1 gm. per cent; globulin 2.7 gm. per cent; cephalin-cholesterol flocculation test, 1 plus in twenty-four hours, 3 plus in forty-eight hours. On symptomatic treatment the mental symptoms cleared and the size of the liver decreased rapidly. The course was afebrile after the day of admission. The concentration of serum lipids dropped precipitously, becoming normal within two weeks. The etiology of the abdominal pain was not investigated. The tentative diagnosis was atypical hepatitis.

CASE II. H. C. (A84592), a thirty-eight year old Negro man, was admitted to the hospital for the first time on July 6, 1951, with crampy abdominal pain of two days' duration and vomiting for twelve hours. He had been a heavy drinker for many years. He had suffered fat intolerance for eight years and had had episodes of epigastric distress for two years. He had had several previous attacks of acute abdominal pain following heavy alcohol consumption. The present attack also was precipitated by a bout of excessive drinking. He was not jaundiced. The abdomen was tender and distended, and x-ray examination revealed an enlarged liver. On the day of admission the serum was noted to be markedly lactescent. Serum amylase was 70 units, bilirubin, 1.68 per cent; alkaline phosphatase, 6.9 Bodansky units. An exploratory laparotomy was performed on July 7, 1951, at which time acute pancreatitis was discovered. Following opera-

tion the serum lipids dropped precipitously. There was no increase in serum amylase. The patient recovered uneventfully and was discharged with instructions to follow a low fat diet (20 gm. a day). However, he soon abandoned his diet and resumed his former drinking habits.

Fourteen months later, following consumption of more than a quart of whisky in a day, he had severe periumbilical pain and vomiting which led to his second admission on September 14, 1952. Temperature was 101°F. Abdominal examination revealed some generalized tenderness with considerable guarding but no true spasm or rigidity. The liver was palpated 4 fingerbreadths below the right costal margin. There was no edema. Once again the serum was lactescent. The leukocyte count was 7,000 per cu. mm. Total serum bilirubin was 2.22 mg. per cent, alkaline phosphatase, 6.4 Bodansky units; bromsulphalein retention, 22 per cent in forty-five minutes; serum amylase, 65 units. The patient improved on conservative therapy and was discharged on September 24, 1952, with instructions to follow a low fat diet. When seen in the clinic in 1955 for incidental complaints he appeared well, although details of the interval history were not obtained.

Case III. H. K. (37-62-54), a forty-two year old white man, was admitted to the hospital on August 25, 1952, with severe pain in the epigastric and left lower quadrant of the abdomen radiating to the left shoulder. The patient was a chronic alcoholic and had suffered several attacks of epigastric pain following drinking bouts during the preceding two years. Eighteen months previously he allegedly had had viral hepatitis. The present admission was preceded by the intake of a large amount of wine. On examination he had a temperature of 102°F. and was slightly jaundiced. There was considerable abdominal spasm and tenderness. The liver could be palpated 3 fingerbreadths below the right costal margin. On admission the leukocyte count was 8,500 per cu. mm., total serum bilirubin, 1.38 mg. per cent; alkaline phosphatase, 8.5 Bodansky units; cephalin-cholesterol flocculation, 3 plus in twenty-four hours; total proteins, 6.4 gm. per cent; albumin, 3.7 gm. per cent; globulin, 2.7 gm. per cent. The serum amylase level on the morning of admission was 106 units, and that evening 76 units. The lipids which were initially elevated to lactescent levels subsequently dropped to abnormally low concentrations. The presumptive diagnosis was acute pancreatitis. On September 3, 1952, biopsy specimen of the liver showed 2 plus fatty infiltration and slight pericholangitic and portal fibrosis. The patient improved on conservative therapy and was discharged on September 11, 1952. When seen in the emergency room for a laceration on October 12, 1954, he appeared to be well.

Case IV. C. B. (58575), a forty-three year old Negro man, was admitted to the hospital on October 22, 1955 because of severe non-radiating pain in the left upper quadrant of the abdomen for four days and vomiting for two days prior to admission. He was an alcoholic of long standing and had suffered *grand-mal* epileptic seizures for eight years. During a previous admission in 1951 for pain in the right upper quadrant of the abdomen x-ray studies of the gastrointestinal tract and gall bladder and a serum amylase determination were normal. Following an alcoholic episode in 1952 he was admitted to another hospital where a diagnosis of acute pancreatitis was made. The serum, which was noted to be lactescent, was sent to this laboratory for analysis. (Table I.) Following this illness the patient had repeated episodes of pain in the left upper quadrant, one of which led to the present admission. The presence of hallucinations and tremulousness on admission suggested a recent alcoholic episode although the patient denied this. On examination he appeared acutely ill. The temperature was 102°F. There was severe generalized abdominal spasm. The abdomen was tympanitic and tender. The liver could be percussed 2 fingerbreadths below the right costal margin. There were muscular cramps suggesting tetany. On admission the serum was noted to be markedly lactescent. The leukocyte count was 12,000 per cu. mm.; serum amylase, 155 units; blood sugar, 120 mg. per cent; total bilirubin, 0.40 mg. per cent; bromsulphalein retention, 38 per cent in forty-five minutes; cephalin-cholesterol flocculation, 3 plus in twenty-four hours; alkaline phosphatase, 6.8 Bodansky units; total protein, 5.4 gm. per cent; albumin, 2.7 gm. per cent; globulin, 2.7 gm. per cent; calcium 6.8 mg. per cent; phosphorus, 4.1 mg. per cent. X-rays of the abdomen taken on admission showed intraperitoneal fluid with localization suggesting acute pancreatitis. A gastrointestinal x-ray study made on November, 2, 1955, revealed an extrinsic mass, probably the pancreas, pressing on the stomach. The gall bladder failed to visualize on cholecystography. The serum became clear within two days. On November 4, 1955, the total bilirubin was 0.42 mg. per cent, bromsulphalein retention, 9 per cent in forty-five minutes; cephalin-cholesterol flocculation test, 0 in twenty-four hours; thymol turbidity, 1.6 units; thymol flocculation, 0; alkaline phosphatase, 6.8 Bodansky units; serum amylase, 166 units; serum calcium, 10 mg. per cent; phosphorus, 5.6 mg. per cent. The patient received parenteral fluids for three days, after which oral feedings were resumed. He improved on conservative therapy, and was discharged on November 7, 1955.

Case V. L. B. (93704), a forty year old white man, was admitted to a nearby hospital on August 18, 1953, for investigation of epigastric discomfort described as "tightness," which had bothered him for five years. A cholecystogram three years previously had been normal. The patient was in the habit of drinking a quart of beer and several glasses of whiskey daily, and more on weekends. He had consumed considerable alcohol

the day before admission. Dietary intake was said to be good. He had noted swelling of his ankles recently. On admission he was obese, florid, extremely nervous and tremulous. There were spider nevi on the face and shoulders, and palmar erythema. The abdomen was obese and slightly tender in the right upper quadrant where a smooth liver edge was felt 5 fingerbreadths below the costal margin. There was pitting edema of both feet. On admission the serum was noted to be very lactescent. Two days later the serum which had cleared considerably was analyzed at this laboratory. The results are shown in Table I. The blood count, urine, stool, and glucose tolerance were normal. On August 25 when the serum had completely cleared, the icterus index was 11, alkaline phosphatase 8.5 Bodansky units; total protein, 6.1 gm. per cent; albumin, 3.8 gm. per cent; globulin, 2.3 gm. per cent; total bilirubin, 0.6 mg. per cent. The serum amylase was not determined. An x-ray study of the gastrointestinal tract on August 20, 1953, was negative except for calcified nodes in the left mid-abdomen. The patient's course in the hospital was uneventful except for daily elevations of temperature to 100 or 101°F. He was able to eat a regular diet from the day of admission. He was discharged on August 28, 1953, with a provisional diagnosis of early Laennec's cirrhosis.

COMMENTS

The cases reported here had a number of features in common, the most striking of which were the marked hyperlipemia and lactescence on admission to the hospital and the rapid clearing of the serum within a few days. As indicated in Table I all lipid components were increased, but the most impressive elevations were in the triglyceride (neutral fat) fraction which initially greatly exceeded the normal range of 0 to 6 mEq./L. The ratio of free to total cholesterol also was elevated, possibly as a consequence of accompanying disease of the liver, although an increase in the ratio has been observed in familial hyperlipemia in the absence of hepatic injury [*1,4*]. This could be accounted for by the finding that in lipemic states most of the serum cholesterol occurs in low density betalipoproteins which characteristically have a ratio of free to total cholesterol of 0.5 to 0.6 [*10*].

All five patients had a history of chronic alcoholism and a bout of excessive drinking immediately prior to hospital admission. In the two patients with multiple attacks of abdominal pain, alcohol was the precipitating factor in each instance. Although the state of nutrition was good in all but one, the patients exhibited evidence of mild hepatic injury consistent with either alcoholic fatty liver or early Laennec's cirrhosis.

Epigastric or abdominal pain on the left side was a significant complaint in every case. Although the serum amylase was not elevated in Cases II, III, and IV, the diagnosis of acute pancreatitis was established by exploratory laparatomy performed in Case II and was made on clinical grounds, but not proved, in Cases III and IV. In Cases I and V, the etiology of the pain was not determined but the possibility of pancreatitis was neither considered nor investigated. In retrospect acute pancreatitis would appear to be the most likely basis for both the abdominal pain and serum lactescence in these patients. Certainly it is one of the more important causes of unexplained abdominal pain in alcoholic patients [*11*] and is often overlooked. Indeed, the frequent occurrence of elevated levels of serum amylase following excessive drinking [*12,13*] suggests that pancreatitis may develop in the absence of pain. The importance of alcoholism in the etiology of pancreatitis [*14*] and the high postmortem incidence of pancreatic lesions in chronic alcoholic patients [*15,16*] strengthens this interpretation.* The occasional marked lipemia of patients with alcoholic fatty liver alluded to by Keefer and Fries [*17*] may likewise have been caused by undiagnosed pancreatitis.

The relationship between pancreatitis and hyperlipemia is a puzzling one. Evidence has been presented to show that at least in one group of young persons hyperlipemia is a chronic hereditary disorder that, in some unknown way, gives rise to acute pancreatitis [*4*]. In addition, however, there are cases such as those reported here in which the hyperlipemia appears to be a transient phenomenon secondary to the pancreatitis. It is assumed that in these cases the onset of hyperlipemia coincides with the development of the pancreatic lesion, and that once the serum clears the lipids remain at a normal level unless there is a recurrence of pancreatitis. In a few such cases, not included in this report, normal concentrations of serum lipids have been found in the intervals between attacks. Unfortunately, no studies had been carried out within a few days or weeks prior to the onset of pancreatitis, so that the transient nature of the

* The normal serum amylase in the cases presented is not incompatible with the diagnosis of acute pancreatitis. In fifty-five cases of acute pancreatitis reported by O'Brien and Thayer [*14*] the amylase was elevated during the course of the disease in only 65 per cent.

hyperlipemia and its precise coincidence with the onset of pancreatitis have not been firmly established. Nevertheless, the long periods of freedom from hyperlipemia, despite an unlimited fat intake, and the absence of xanthomatous lesions clearly distinguish these persons from those with familial hyperlipemia and secondary pancreatitis.

It has been postulated that acute pancreatitis may give rise to hyperlipemia in either of two ways; by creating a disturbance in lipid metabolism [*18*], or by making it possible for liquefied fat in the retroperitoneal space to gain access to the circulation [*6*]. In addition, recent studies on the normal fat-clearing mechanism raise the question of whether or not alterations in the chemical or physical properties of the serum albumin may be involved in the accumulation of blood lipids.

The role of the pancreas in fat metabolism has been studied extensively since the observation that fatty livers develop in depancreatized dogs maintained on insulin [*19,20*]. It is now well known that the fatty infiltration under these conditions is due to a deficiency of choline and other lipotropic substances resulting from the incomplete digestion and absorption of dietary protein in the absence of the proteolytic enzymes of the external secretions of the pancreas [*21,22*]. As fat accumulates in the liver the serum lipids tend to fall [*23,24*], an effect presumably due to hepatocellular dysfunction and malnutrition. However, Dragstedt et al. [*25*] have reported that hyperlipemia develops over a period of several weeks in depancreatized dogs which have been treated with insulin if the presence of minimal amounts of pancreatic juice in the intestinal tract is assured, either by sparing a fragment of pancreas and permitting its external secretion to enter the intestine, or by feeding the dogs raw pancreas. These observations have been interpreted as evidence that the pancreas has an internal secretion (lipocaic) which plays a role in the regulation of the serum lipids, and that the absence of this hormone leads to hyperlipemia provided dietary absorption is adequate. Entenman, Chaikoff and Montgomery [*24*] also found an elevation of serum lipids when raw pancreas was fed to depancreatized dogs treated with insulin, a phenomenon which could not be induced by feeding raw pancreas to normal animals. While this phenomenon has not been explained, most investigators [*21,22*] deny the existence of lipocaic. If the hyperlipemia associated with acute pancreatitis in man were due to a deficiency of lipocaic, it would have to be assumed that the deficiency state antedated the onset of acute pancreatitis, since in Dragstedt's experiments [*25*] hyperlipemia did not develop for at least a month following partial pancreatectomy. While this possibility cannot be excluded with certainty, since the precise time relationship between the onset of acute pancreatitis and the appearance of hyperlipemia is not known, it appears unlikely in view of (1) the prompt appearance of serum lactescence following experimental injury of the pancreas [*8*], (2) the absence of hyperlipemia in the intervals between attacks of relapsing pancreatitis in the few patients that have been studied, and (3) the failure of hyperlipemia to develop in persons with chronic pancreatic insufficiency many of whom still secrete small amounts of enzyme. The prompt fall in serum lipids following an attack of acute pancreatitis could conceivably, on the basis of Dragstedt's observations, be related to complete suppression of pancreatic secretion in a person with an antecendent deficiency of lipocaic. Thus Dragstedt et al. [*25*] observed that the hyperlipemia in partially depancreatized dogs cleared following external diversion of the secretions of the pancreatic remnant, an effect that was noted within a week or two. Unfortunately the serum lipids were not investigated any earlier, so that it is not known whether or not they fell as promptly as they do following an attack of acute pancreatitis.

Since hyperlipemia is known to occur in patients with diabetic acidosis, the question arises whether or not the increase in serum lipids associated with acute pancreatitis may be due to a disturbance in carbohydrate metabolism. Certainly mild diabetes is a relatively common complication of acute pancreatitis and, indeed, it has been encountered in a few patients with hyperlipemia [*26*]. However the absence of glycosuria in many instances, as in the present study, and the relatively mild character of the diabetes make it unlikely that the hyperlipemia of acute pancreatitis is the result of a disturbance in insulin production.

In view of the implication of an internal secretion of the pancreas other than insulin in the regulation of serum lipids it is of interest that glucagon, the hyperglycemic factor produced by the alpha cells of the pancreas, reduces alimentary lipemia [*27*]. Administration of carbohydrate will similarly reduce alimentary

lipemia [*28*]. Conversely, destruction of the alpha cells with cobaltous chloride is followed by a gradual increase in serum lipids [*29*]. However, a deficiency of glucagon cannot account for the type of hyperlipemia which is seen in acute pancreatitis unless it is shown to be gradual and not, as generally assumed, an acute result of the pancreatitis.

Recent evidence indicates that the dietary content of unsaturated fatty acids is one of the factors that determines the level of the serum lipids [*30,31*]. Since the intestinal hydrolysis of oils containing unsaturated fatty acids requires the presence of pancreatic juice [*32*], the question arises as to whether or not the hyperlipemia of pancreatitis may be due to a deficiency of available unsaturated fatty acids related to a decrease in pancreatic secretion. However, the evanescent character of the serum lipid changes in acute pancreatitis, and the striking absence of hyperlipemia in patients with frank pancreatic insufficiency, following either pancreatectomy or chronic pancreatitis, would appear to be inconsistent with this hypothesis.

Serum albumin plays an important role in the mechanism for removing excess fat from the blood. Normally the triglycerides entering the plasma are hydrolyzed enzymatically by a clearing factor, resulting in the release of non-esterified fatty acids. The latter are promptly bound by albumin, the presence of which is necessary for the hydrolysis of plasma triglycerides [*33–35*]. If serum albumin is depressed as a result of nephrosis or plasmapheresis, hyperlipemia ensues, an effect that can be abolished by infusing albumin [*3*]. Thus albumin, through its role as a fatty acid acceptor, appears to be an integral part of the clearing mechanism. Theoretically, therefore, an alteration in the binding capacity of albumin, a change in the chemical or physical state of the free fatty acids arising during the course of intravascular hydrolysis, or a defect in the production or release of clearing factor could produce hyperlipemia. These possibilities have not been explored in the case of acute pancreatitis. However, a recent report [*36*] suggests a correlation between elevated lipids and the defect of calcium metabolism commonly found in patients with pancreatitis. Combination of non-esterified fatty acids with calcium instead of with albumin might impede the clearing of triglyceride from the serum.

A convincing argument can be made for the theory that the hyperlipemia of acute pancreatitis is due to embolization of liquefied fat arising at the site of necrosis. Indeed, several investigators [*6,37*] have demonstrated pools of fat entering injured vessels in the areas of necrosis, and the presence of fat emboli in the kidneys and lung and has suggested that the latter may be responsible for renal failure and cyanosis which often accompany acute hemorrhagic pancreatitis. Unfortunately, the serum lipids were not analyzed in any of these cases, except in one instance in which [*6*] the blood was thought to be hyperlipemic on gross inspection at autopsy. It has been suggested that the entry of lipid into the circulation may be related to the digestion of interlobular and peripancreatic fat by lipase and the release of oleic acid which is liquid at body temperature [*6*]. However, the staining properties of the lipid found in areas of pancreatic necrosis and in fat emboli are those of triglyceride. This suggests that embolization of fat is probably more closely related to the injury of adipose tissues and vessels than to the release of free fatty acid. The possibility that the emboli in such cases are secondary to the hyperlipemia is worthy of comment. In a previous report [*4*] indirect evidence was presented in support of the theory that the fat emboli in patients with diabetic acidosis and certain other hyperlipemic states may be derived from the serum lipids. The possible potentiating effect of hyperlipemia on thrombosis [*38*] constitutes an additional mechanism by which abnormally high concentrations of serum triglycerides might precipitate local injury. However, in the type of acute pancreatitis under consideration the histologic demonstration of lipid pools entering damaged vessels at sites of pancreatic necrosis strongly suggests that the emboli arise from foci of necrotic adipose tissue. Although there is no direct evidence to show that such embolization leads to hyperlipemia, the remarkable case of MacMahon and Weiss [*39*] provides a graphic illustration of how the entry of fat into the circulation from an area of necrosis may affect the serum lipids. In this instance the necrotic lesion was in an alcoholic fatty liver and was due to carbon tetrachloride poisoning. At autopsy the blood in the right side of the heart and large pulmonary arteries contained fat which on standing rose to the top as a layer constituting 60 per cent of the total blood volume, while the vessels elsewhere contained much less fat. The occurrence of the fat only in the right side of the circulation suggests that

the necrotic fatty liver was the source of the hyperlipemia.

The hyperlipemia of acute pancreatitis is accompanied by increases of serum cholesterol and phospholipid (Table 1), a phenomenon observed in other forms of hyperlipemia [*1,4*]. Since the infusion of triglyceride and lecithin in experimental animals leads rapidly to hypercholesteremia [*40*], it appears likely that the latter is secondary to the elevated triglycerides.

SUMMARY

Marked but transient lactescence of serum has been noted in patients with abdominal pain following bouts of acute alcoholism. The evidence presented suggests that the hyperlipemia and abdominal pain were due to acute pancreatitis. The possible interrelationship between pancreatitis and hyperlipemia is discussed.

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The Pattern of Intermediary Carbohydrate Metabolism in Cushing's Syndrome*

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IN previous studies we have observed unique disturbances in intermediary carbohydrate metabolism in a small group of patients receiving 17-hydroxycorticosteroids and in patients with Cushing's syndrome during ether anesthesia [*1,2*]. In the present study these observations have been confirmed and extended to include a variety of experimental metabolic conditions in patients with confirmed Cushing's syndrome and in patients receiving 17-hydroxycorticosteroid therapy. Blood concentrations of glucose, intermediary carbohydrate metabolites, lipids, ketones and inorganic phosphorus in these patients have been compared to the concentrations of these substances in normal subjects and in patients with mild to moderate diabetes mellitus, with and without associated obesity.

MATERIAL AND METHODS

The biochemical technics used are summarized in Table I. The patients and the experimental conditions are summarized in Table II.

The "diabetic" patients had a degree of glucose intolerance (mild to moderate, American Diabetes Association standards) similar to that observed in patients with Cushing's syndrome. The group included subjects in whom the diagnosis of Cushing's syndrome was entertained by reason of certain clinical features such as obesity, amenorrhea, hirsutism, fatigue, arteriosclerosis and hyperlipemia. Two patients with severe diabetes mellitus were studied to confirm reported observations on blood lactic and pyruvic acid, and inorganic phosphorus concentrations [*4–7*].

Glucose utilization was evaluated by American Diabetes Association standards for normal changes in glucose concentrations. In addition, measurements of carbohydrate intermediary metabolites and serum total inorganic phosphorus were made in thirty normal subjects. The changes in these subjects confirm those reported in the literature [*4,8–10*].

The dose and duration of treatment prior to testing of the patients who received 17-hydroxycorticosteroid therapy are shown in Table III.

Several technical and dietary precautions are essential in order to be reasonably certain that the experimental conditions are comparable from one subject to the next: (1) Patients must eat 300 to 350 gm. of carbohydrate per day for at least three days prior to the morning of the test. A twelve- to fifteen-hour fast precedes the test. (2) Patients must lie quietly in bed throughout the test. (3) Venous blood samples must be taken with a minimum of stasis, preferably without a tourniquet. (4) Blood samples for lactic and pyruvic acid determinations should be treated with protein precipitants immediately after being drawn. If plasma lactic acid is to be measured, the blood should be placed in cold test tubes containing iodoacetic acid and the protein precipitated with cold 10 per cent trichoroacetic acid within a half-hour [*11*]. (5) The patient should be assessed for nervousness and apprehension since higher than normal fasting concentrations of lactate and pyruvate and lower than normal fasting concentrations of serum total inorganic phosphorus may result from a reflex release of epinephrine immediately prior to the start of the test period [*12*].

RESULTS

Fasting Concentrations. (Table IV.) Observations in patients with Cushing's syndrome and in those receiving 17-hydroxycorticosteroid therapy have been combined unless otherwise indicated since no significant differences were found between the two groups; both groups demonstrated the same differences from normal subjects.

Only two patients with Cushing's syndrome and one receiving 17-hydroxycorticosteroid therapy had fasting hyperglycemia. Patients with mild to moderate diabetes mellitus had higher than normal glucose levels ($p < .01$).

Patients with Cushing's syndrome and subjects receiving 17-hydroxycorticosteroids had strikingly elevated blood concentrations of

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lactate and pyruvate. No difference in lactate or pyruvate levels was observed between the normal subjects and the patients with mild to moderate diabetes mellitus. The increase in fasting concentrations of lactic and pyruvic acids was observed as early as the tenth day of 17-hydroxycorticosteroid therapy and preceded the appearance of glucose intolerance. Subtotal adrenalectomy in cases of Cushing's syndrome was associated with a return of blood lactate and pyruvate to normal levels. (Table v.)

TABLE I
METHODS

Substance Measured	Technic
Total inorganic phosphorus (serum)	Fiske-SubbaRow *J. Biol. Chem.* 66: 375, 1925
True glucose (whole blood)	Nelson-Somogyi *J. Biol. Chem.* 153: 375, 1944
Lactic acid (plasma or whole blood)	Barker-Summerson *J. Biol. Chem.* 138: 535, 1941
True pyruvate* (whole blood)	Seligson-Shapiro (chromotography) *Anal. Chem.* 24: 754, 1952
Citric acid (serum)	Elliott modification of Natelson et al. *J. Biol. Chem.* 175: 745, 1948
Alpha-keto glutaric acid (whole blood)	Same as for true pyruvate
Ketones (β-hydroxybutyric and aceto-acetic acids and acetone whole blood)	Greenberg-Lester *J. Biol. Chem.* 154: 177, 1944
Blood lipids:	
Total fatty acids	Stoddard-Drury *J. Biol. Chem.* 84: 721, 1929
Cholesterol and esters	Bloor-Knudson *J. Biol. Chem.* 27: 107, 1916 Bloor *J. Biol. Chem.* 24: 227, 1916
Lipid phosphorus	Bloor *J. Biol. Chem.* 36: 33, 1918 Fiske-SubbaRow *J. Biol. Chem.* 66: 375, 1925

* This chromatographic technic gives lower values for both the normal fasting concentrations and the normal changes following the administration of glucose than the values obtained by the Friedemann-Haugen method (*J. Biol. Chem.*, 147: 415, 1943).

TABLE II
MATERIAL AND EXPERIMENTAL CONDITIONS

Fasting:
- Twelve to fifteen hour overnight fast following three to five days of a high (350 gm./day) carbohydrate diet
  - Thirty normal adult men and women, ages twenty-three to sixty-five, all women with normal menstruation
  - Sixteen patients with clinically confirmed Cushing's syndrome
  - Eleven patients receiving 17-hydroxycorticosteroid therapy (six with pemphigus, two with exfoliative dermatitis, one with chronic berylliosis, one with metastatic mammary carcinoma, one with intrinsic asthma)
  - Eleven patients with mild to moderate diabetes mellitus: those requiring insulin received none for twenty-four to forty-eight hours prior to the day of the test
  - Eleven patients with gross obesity, four of these included in diabetes mellitus group, seven of these included in normal group
  - Eight patients with severe cirrhosis
  - Six patients with adrenal hyperplasia of types other than Cushing's syndrome; three of these were obese

Oral glucose tolerance tests:
- One hundred gm. of glucose were administered orally following twelve to fifteen hour overnight fast and a high carbohydrate diet.
  - Thirty normal adults, seven of whom were grossly obese
  - Five patients with confirmed Cushing's syndrome
  - Ten patients receiving 17-hydroxycorticosteroid therapy
  - Eight patients with diabetes mellitus, with and without obesity
  - Two patients with severe diabetes mellitus
  - Five patients with adrenal hyperplasia of types other than Cushing's syndrome

Intravenous L (+) lactate infusion:
- Seventy-five mg./kg. body weight infused as a 14 per cent solution over a period of two minutes [*3*].
  - Twelve normal subjects
  - Eleven patients with Cushing's syndrome
  - Twelve patients with gall bladder disease
  - Fourteen patients with moderate to severe cirrhosis

Ether anesthesia:
- Fasting
  - Twenty-two normal adults
  - Eight patients with Cushing's syndrome
- Intravenous glucose administration (0.5 gm./kg. as 20 per cent solution)
  - Twelve normal adults
  - Three Cushing's syndrome

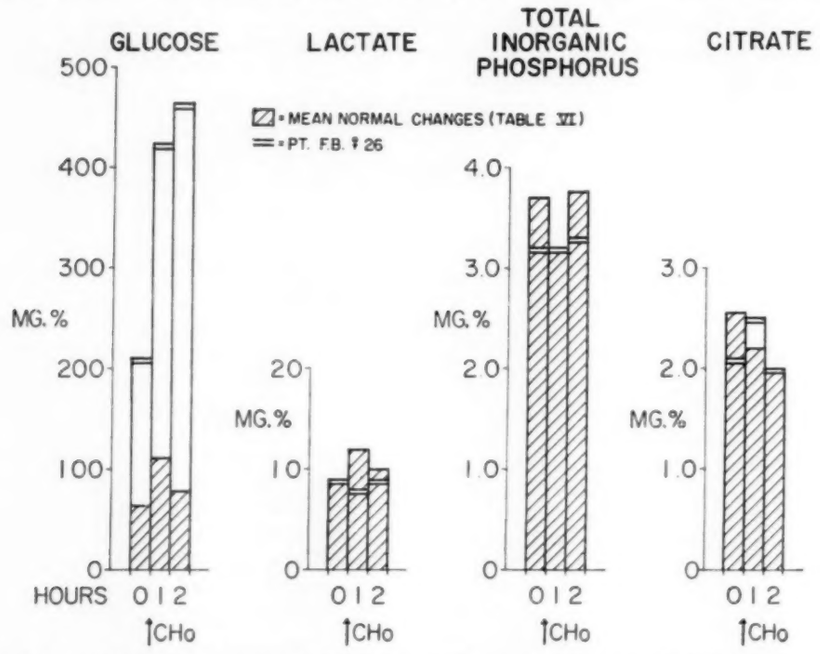

FIG. 1. Abnormal responses in blood (or serum, see Table I) to administered glucose in a patient with severe diabetes mellitus. Pyruvate changes (not shown) were also less than normal.

TABLE III

DOSE AND DURATION OF TREATMENT PRIOR TO TESTING OF PATIENTS WHO RECEIVED 17-HYDROXYCORTICOSTEROID THERAPY

Case (No.)	Age (yr.) and Sex	Hormone	Dose (mg./day)	Duration	Diagnosis
I	49, M	Prednisone	10	10 days	Pemphigus
II	69, M	Cortisone	800–600	2 mo.	Pemphigus
		Prednisone	120– 60	4 mo.	
III	54, M	Cortisone	.....	.....	Pemphigus
		Prednisone			
IV	67, F	Cortisone	500	1 mo.	Pemphigus
		Prednisone	80–30	4 mo.	
V	60, F	Prednisone	150– 80	10 days	Pemphigus
			80– 30	13 days	
VI	49, F	Prednisone	40	2 wk.	Pemphigus
VII	37, F	Prednisone	200– 40	2 wk.	Exfoliative dermatitis
VIII	74, M	Cortisone	250–200	1 mo.	Exfoliative
		Prednisone	120– 30	2 wk.	dermatitis
IX	35, F	Cortisone	200	2 yr.	Chronic berylliosis
X	52, F	Cortisone	200	7 mo.	Metastatic carcinoma of the breast
XI	45, F	Cortisone	200	1 yr.	Intrinsic asthma

Fasting concentrations of citric and alpha-ketoglutaric acids were normal in patients with diabetes mellitus, Cushing's syndrome, and in patients receiving 17-hydroxycorticosteroid therapy. This finding was in contrast to our observations in severe cirrhosis (see page 41).

Blood ketone concentrations were normal in all patients including those with diabetes mellitus. The high carbohydrate diet, the short fasting period, and the mildness of the diabetes mellitus probably account for this finding.

Changes in blood lipid concentrations were not constant; abnormally increased levels of total cholesterol (>280 mg. per cent) and cholesterol esters were observed in five of seven patients with Cushing's syndrome and in patients receiving corticosteroid therapy; normal levels of total fatty acids (<480 mg. per cent) and lipid phosphorus (<11.5 mg. per cent) were present in these same seven subjects. Patients with mild to moderate diabetes mellitus also had elevated cholesterol and cholesterol ester concentrations (mean cholesterol of 345 mg. per cent); in addition, half of these patients had increased total fatty acid and lipid phosphorus concentrations.

While on a high carbohydrate diet, fasting blood levels of inorganic phosphorus were less than 3.1 mg. per cent in all patients with Cushing's syndrome and corticosteroid-induced diabetes who were tested in our laboratory. However, in ten additional patients with Cushing's syndrome tested by other laboratories while they were not on a high carbohydrate diet, only two patients had concentrations less than 3.1 mg.

TABLE IV

VENOUS BLOOD FASTING CONCENTRATIONS OF CARBOHYDRATE METABOLITES, KETONE BODIES AND SERUM TOTAL INORGANIC PHOSPHORUS IN NORMAL ADULTS AND PATIENTS WITH DIABETES MELLITUS, CUSHING'S SYNDROME AND 17-HYDROXYCORTICOSTEROID THERAPY

Substance	Normal Adults				Patients with Diabetes Mellitus Mild or Moderate				Patients with Cushing's Syndrome or 17-Hydroxycorticosteroid Therapy				
	No. of Patients	Range (mg. %)	Mean (mg. %)	Standard Error (mg. %)	No. of Patients	Range (mg. %)	Mean (mg. %)	Standard Error (mg. %)	No. of Patients	Range (mg. %)	Mean (mg. %)	Standard Error (mg. %)	P value
Glucose	26	56–93	80	±2.3	10	75–220	112	±10	26	59–180	84	±4.4	<.01*
Lactate	26	3–11	8.0	0.50	10	5–14	9.0	0.8	16†	8–38	16	2.0	<.001‡
									10§	15–30	19	1.5	<.001‡
Pyruvate	27	0.6–1.5	1.0	0.07	8	0.9–1.3	1.1	0.08	13	1.8–3.3	2.4	0.13	<.001‡
Citrate	30	0.7–4.0	2.3	0.12	18	1.0–3.6	2.3	0.18	10	0.6–3.7	1.6	0.32	Not significant
Alpha-keto glutarate	17	0.04–0.16	0.09	0.01	9	.07–0.18	0.12	0.015	8	.05–.17	0.12	0.014	Not significant
Ketones	15	0.4–2.3	1.3	0.15	12	0.4–1.5	0.90	0.15	9	0–1.5	1.0	0.18	Not significant
Inorganic phosphorus	30	2.9–4.1	3.5	0.06	10	2.8–3.5	3.2	0.06	15	2.4–3.7	2.9	0.1	<.01‡

* As compared with normal subjects.
† Sixteen patients confirmed Cushing's syndrome.
‡ As compared with normal and diabetic subjects.
§ Ten patients on 17-hydroxycorticosteroid Rx.

per cent. This effect of a high carbohydrate diet was further studied in four patients with Cushing's syndrome who were tested both while they were on and off a high carbohydrate diet; three of these patients had serum inorganic phosphorus concentrations of more than 3.1 mg. per cent while they were off the diet and less than 3.1 mg. per cent while they were on the diet. Blood inorganic phosphorus concentrations were normal in the patients with diabetes mellitus.

Oral Glucose Tolerance Tests. Although fasting concentrations of blood glucose were normal in twenty-four of twenty-seven patients with Cushing's syndrome or 17-hydroxycorticosteroid-induced diabetes, all but one of fifteen tested demonstrated decreased utilization of administered oral glucose. (Table VI.) The single patient who failed to demonstrate glucose intolerance had received 10 mg. per day of prednisone for ten days; blood lactic and pyruvic acid concentrations were already elevated at this time.

The degree of decreased utilization observed in these patients was not statistically significantly different from that of the patients with mild to moderate diabetes mellitus ($p > .05$), but was significantly different from the normal subjects.

The patients with Cushing's syndrome and those receiving 17-hydroxycorticosteroid therapy demonstrated, in addition to fasting hyperlacticemia and hyperpyruvicemia, a greater than normal increase in the concentration of these organic acids following the oral administration of glucose. Patients with mild to moderate diabetes mellitus demonstrated no abnormalities. The two patients with severe diabetes mellitus had less than the normal response of lactate and pyruvate to administered glucose, as reported by others [*4–7*]; a typical case is shown in Figure 1.

The changes in blood citrate concentrations were variable in all groups studied except the normal group, in which there was a significant decrease in seventeen of eighteen subjects studied. The maximal fall was observed at either the one- or two-hour period and ranged from a fall of 0.5 mg. per cent to 2.5 mg. per cent. These changes in normal subjects have been reported previously [*8,10*].

The concentrations of blood citrate rose one hour after the administration of glucose in five of nine patients with mild to moderate diabetes mellitus and in the two patients with severe diabetes. The presence or absence of this abnormality could not be correlated with either the degree of glucose intolerance or the clinical course of the patient [*13*]. The changes were normal in the five patients with corticosteroid-induced diabetes, but two of four patients with Cushing's syndrome had increases of 1.0 mg. per

TABLE V

EFFECT OF SEVEN TO TWENTY-THREE DAYS OF PREDNISONE THERAPY AND OF SUBTOTAL ADRENALECTOMY ON FASTING CONCENTRATIONS OF LACTATE AND PYRUVATE

Case and Diagnosis	Fasting Concentration Plasma Lactate (mg. %)		Fasting Concentration Blood Pyruvate (mg. %)		Days of Therapy	Hormone	Dose (mg./day)
	Before Therapy	After Therapy	Before Therapy	After Therapy			
M. M., Pemphigus	6.0	35	.....	....	10	Prednisone	150–80
	8.0	25	.....	....	23	Prednisone	80–30
J., Pemphigus	6.0	18.3	0.9	2.6	11	Prednisone	10
G., Exfoliative dermatitis	8.0	16.0	1.4	2.5	7	Prednisone	40
				3.3	11	Prednisone	40
C., Exfoliative dermatitis	9.8	13.8	1.3	1.8	14	Prednisone	160–20
S. S., Cushing's syndrome	21.3*	16.5†	1.94*	1.0†	20‡	Cortisone	60
		7.0†		1.0†	27‡	Cortisone	25
		9.3†		1.0†	29‡	Cortisone	25
R. A., Cushing's syndrome	17.2*	11.0†	2.02*	1.15†	111‡	None	.....
	18.1*	.....	1.72*	....	....	.....	.....
	16.0*	.....	1.84*	....	....	.....	.....
S. F., Cushing's syndrome	15.0*	13.5†	1.8*	1.6†	44‡	Cortisone	25
	14.0*	13.3†	1.8*	1.65†	55‡	None	.....
	15.2*	11.5†	2.0*	1.40†	65‡	None	.....
		10.5†			310‡	None	.....
H. B., Cushing's syndrome	13.0*	.....	2.0*	....	....	.....	.....
	13.5*	.....	1.6*	....	....	.....	.....
	12.5*	.....	1.5*	....	....	.....	.....
	.....	.....	1.6*	....	....	.....	.....

* Preoperative
† Postoperative
‡ Days postoperative

cent while the remaining two showed no significant change.

Patients with mild or moderate diabetes mellitus had a delayed decrease in total serum inorganic phosphorus concentrations when compared to normal subjects ($p < .01$); the maximal decrease (0.4 mg. per cent) occurred at one hour in the latter group but at two hours (0.6 mg. per cent) in the diabetic subjects. The patients with corticosteroid-induced diabetes showed greater than normal decreases in serum total inorganic phosphorus concentrations despite the fact that their fasting levels were lower than normal. The per cent change from the fasting level was significantly greater ($p < .01$) than that observed in normal subjects and in the patients with diabetes mellitus.

The abnormalities observed in the venous blood concentrations of glucose, lactate, pyruvate and serum total inorganic phosphorus in patients with Cushing's syndrome following the administration of glucose gradually returned to normal after subtotal adrenalectomy. This reversal of the preoperative abnormalities is shown in Figure 2. The time interval between operation and biochemic reversal was variable but could be correlated with clinical improvement.

TABLE VI

FINDINGS AFTER ADMINISTRATION OF 100 GM. OF GLUCOSE ORALLY

Substance		Normal Subjects			Patients with Diabetes Mellitus			Patients with Cushing's Syndrome 17-Hydroxycorticosteroid Therapy			P value
		Fasting	1 hr.	2 hr.	Fasting	1 hr.	2 hr.	Fasting	1 hr.	2 hr.	
Glucose, (mg. %) whole blood	Mean	65	111	76	112	235	233	78	198	204	Not significant compared to diabetes mellitus; $p < .01$ compared to normal
	No. of Patients	26			11				15†		
	Standard Error	2.0	5.5	5.8	10	28	39	5.9	15.1	23.3	
Lactate, (mg. %) plasma	Mean	7.0	12.0	9.6	9.0	13.0	13.0	16.7	25.0	24.6	<.001*
	No. of Patients	30			11				9‡		
	Standard Error	0.5	0.4	0.5	0.76	1.0	0.82	1.4	2.4	2.2	
Pyruvate, (mg. %) whole blood	Mean	1.12	1.50	1.21	1.1	1.3	1.2	2.2	2.8	2.7	<.001*
	No. of Patients	22			8				7‡		
	Standard Error	0.09	0.06	0.09	0.08	0.20	0.20	0.1	0.2	0.2	
Citrate, (mg. %) serum	Mean	2.44	2.20	1.90	*Variable:* 7 patients rose 0.2–1.3 mg. % at 1 hr., mean rise of 0.7 mg. %; 4 patients fell 0.3–1.2 mg. %, mean fall 0.8 mg. %			3.0	2.2	2.2	
	No. of Patients	17						0.5		5§	
	Standard Error	0.22	0.14	0.12						4‡	
	Mean							1.9	2.6	2.2	
	No. of Patients							4‡			
	Standard Error							0.3			
Ketones, (mg. %) whole blood	Mean	0.7	0.2	0.2	1.1	0.8	0.8	1.3	1.2	1.0	Not significant*
	No. of Patients	6			9				5‖		
	Standard Error	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	
Total inorganic phosphorus, (mg. %) serum	Mean	3.7	3.3	3.7	3.2	3.1	2.6	2.9	2.6	2.3	<.01*
	No. of Patients	15			8				10‡		
	Standard Error	0.11	0.09	0.07	0.09	0.10	0.10	0.12	0.11	0.14	

* P value based on analysis of observed differences in patients with Cushing's syndrome and those receiving 17-hydroxycorticosteroid therapy compared both to (1) normal subjects and (2) to patients with mild to moderate diabetes mellitus.

† 8 with Cushing's syndrome.

‡ 4 with Cushing's syndrome.

§ 5 receiving 17-hydroxycorticosteroid therapy.

‖ 3 with Cushing's syndrome.

Blood ketone concentrations decreased in all groups one to two hours after the administration of glucose.

A decrease in blood fatty acid and lipid phosphorus concentrations was observed in all groups following the administration of glucose; this change was most marked in patients with diabetes mellitus whose fasting concentrations were the most elevated. Significant decrease in total serum cholesterol levels were also observed in normal and diabetic subjects but not in the patients with Cushing's syndrome. (Fig. 3.)

Intravenous Infusion of Sodium L(plus) Lactate. Blood lactic acid concentrations before and after

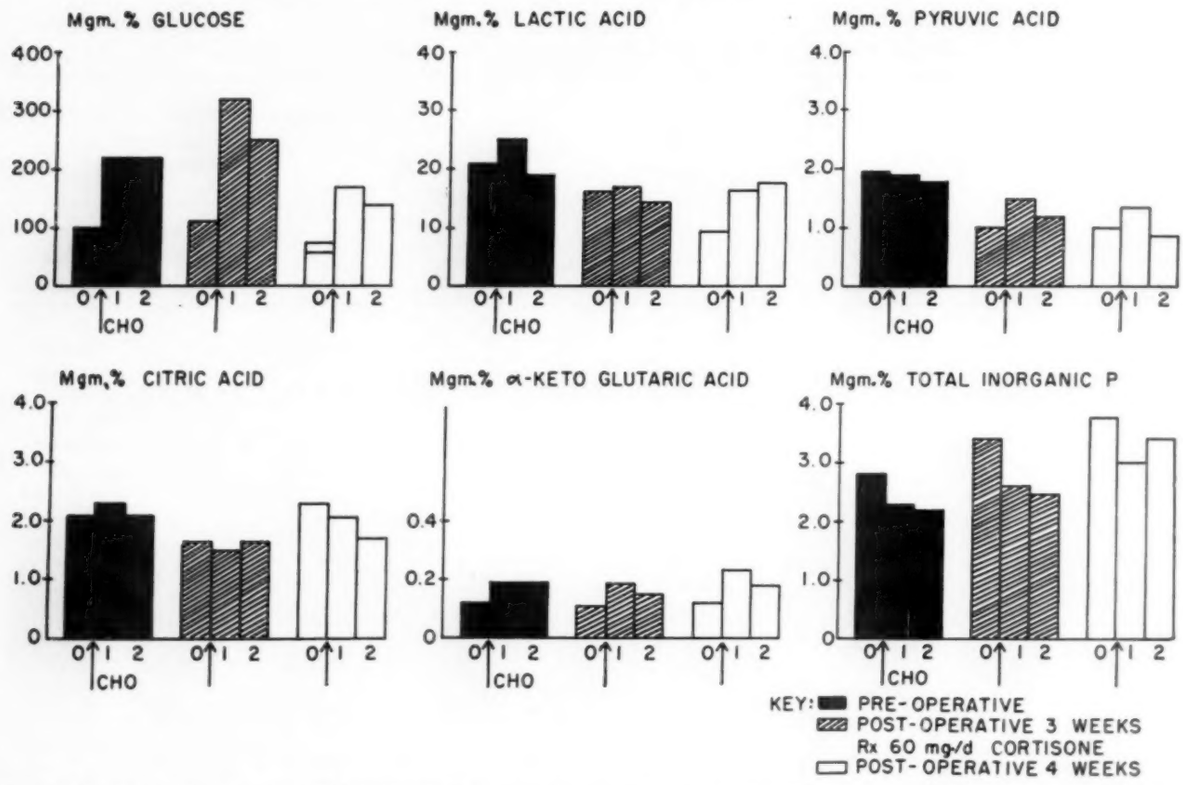

FIG. 2. Gradual return to normal of the fasting and postglucose concentrations of blood metabolites and inorganic phosphorus following successful subtotal adrenalectomy in a patient with Cushing's syndrome.

lactate infusion are shown in Figure 4. Twelve normal adults tested before and thirty minutes after the infusion had less than a 5 mg. per cent increase over the fasting concentration. Patients with gall bladder disease had normal fasting blood lactic acid concentrations and a normal response to a lactate infusion. The results in the patients with cirrhosis were variable: some demonstrated elevated fasting concentrations both with and without abnormal responses to an infusion of lactate, while others had normal values throughout. No correlation could be found between the severity of the cirrhosis and the presence of abnormalities. The patients with Cushing's syndrome had consistently high fasting concentrations and excessive accumulations after the infusion. Those few patients with Cushing's syndrome who had normal fasting levels (Fig. 4) were not on high carbohydrate diets.

Metabolic Consequences of Ether Anesthesia in Cushing's Syndrome. Patients with Cushing's syndrome when fasting and when glucose was administered during ether anesthesia had greater elevations in blood lactic and pyruvic acids and glucose concentrations than did normal subjects. (Fig. 5.) In addition, the administration of glucose during ether anesthesia was associated with a fall in serum total inorganic phosphorus in patients with Cushing's syndrome, in contrast to a striking rise regularly observed in normal subjects [*14,15*].

Metabolic Consequences of Overnight Fast and Administered Glucose in Obesity and Adrenal Hyperplasia of Types Other Than Cushing's Syndrome. Eleven grossly obese subjects were studied; four of these had glucose intolerance of a degree which placed them in the category of mild diabetes mellitus; the remainder were included in the normal group. None of the eleven subjects had abnormal changes in lactate, pyruvate or inorganic phosphate and hence in no way were comparable to the patients with true Cushing's syndrome. One of these eleven was suspected of having Cushing's syndrome and was adrenalectomized but the diagnosis was not confirmed postoperatively.

Four patients with obesity, hirsutism, dia-

betes and increased 17-ketosteroid excretion but without Cushing's syndrome and one patient with adrenogenital syndrome were studied. A second patient with adrenal hyperplasia of the adrenogenital type was tested during pregnancy and while she was off cortisone therapy, and at a time when her urinary 17-ketosteroid concentration was elevated. Three of these patients gave normal results while three had glucose intolerance unassociated with any lactate, pyruvate or inorganic phosphate abnormalities.

Observations in Severe Cirrhosis. Eight patients with severe cirrhosis were studied. The complete data will be published elsewhere [*16*]. The results in these eight subjects indicate that fasting concentrations of lactic and pyruvic acids and of inorganic phosphate varied, but generally were normal; fasting concentrations of citrate were frequently elevated. Greater than normal fasting concentrations of alpha-ketoglutarate were consistently observed and confirmed earlier reports [*17*]: the mean value was 0.27 mg. per cent (standard error 0.04 mg. per cent) with a $p < .001$ when compared to normal subjects and patients with Cushing's syndrome or diabetes mellitus.

COMMENTS

The alterations in glucose, lactic and pyruvic acids, and in inorganic phosphorus metabolism noted in patients with Cushing's syndrome or 17-hydroxycorticosteroid therapy are similar to those previously described in four patients with chronic psychosis and in one normal subject given hydroxycortisone or corticotropin (ACTH) [*2*]. Other investigators have observed alterations in blood lactic and pyruvic acids in Cushing's syndrome and 17-hydroxycorticosteroid therapy, but the number of cases have been few and the results inconsistent [*18–21*]. The difference between the results of the present study and those of other investigators may be related to difficulties in diagnosing Cushing's syndrome and the apparent failure to observe the precaution of a high carbohydrate diet prior to the time of testing.

The unique metabolic pattern which we have observed is presumably due to the effects of an increase in 17-hydroxycorticosteroid hormones. It is uncertain, however, whether the observed changes in carbohydrate metabolism are related to (1) direct effects of 17-hydroxycorticosteroids on protein and fat metabolism, (2) changes in insulin activity in response to adrenal hyperplasia, or (3) a direct effect of 17-hydroxycorticosteroids on glucose utilization.

The decrease in glucose utilization and the elevated concentrations of lactate and pyruvate associated with 17-hydroxycorticosteroid activity have generally been assumed to reflect (1) an

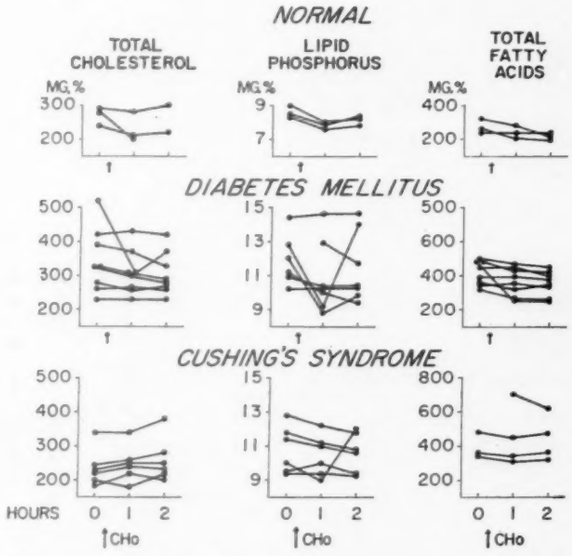

FIG. 3. Changes in blood lipid concentrations following administration of oral glucose to normal subjects, patients with diabetes mellitus, and patients with Cushing's syndrome.

increase in gluconeogenesis from protein and (2) a decrease in the conversion of carbohydrate and acetate to fat [*22,23*]. These activities are presumed not only to increase glycogen stores but also to overload the pathways of carbohydrate metabolism. We believe our observations do not support this hypothesis as the sole mechanism responsible for the increase in lactate and pyruvate concentrations. The normal concentrations of citrate and alpha-ketoglutarate observed, in contrast to the elevated levels in cirrhosis, suggest that the pathways leading to glycogen formation are neither overloaded nor blocked.

Changes in insulin activity in the presence of excess 17-hydroxycorticosteroid activity and an intact pancreas are difficult to study. Our results do not clarify this problem. The differences between patients with Cushing's syndrome and those with diabetes mellitus rule out the possibility of relative lack of insulin as the responsible mechanism in Cushing's syndrome. Similarly, insulin resistance does not appear to explain the alterations in inorganic phosphorus and lactic

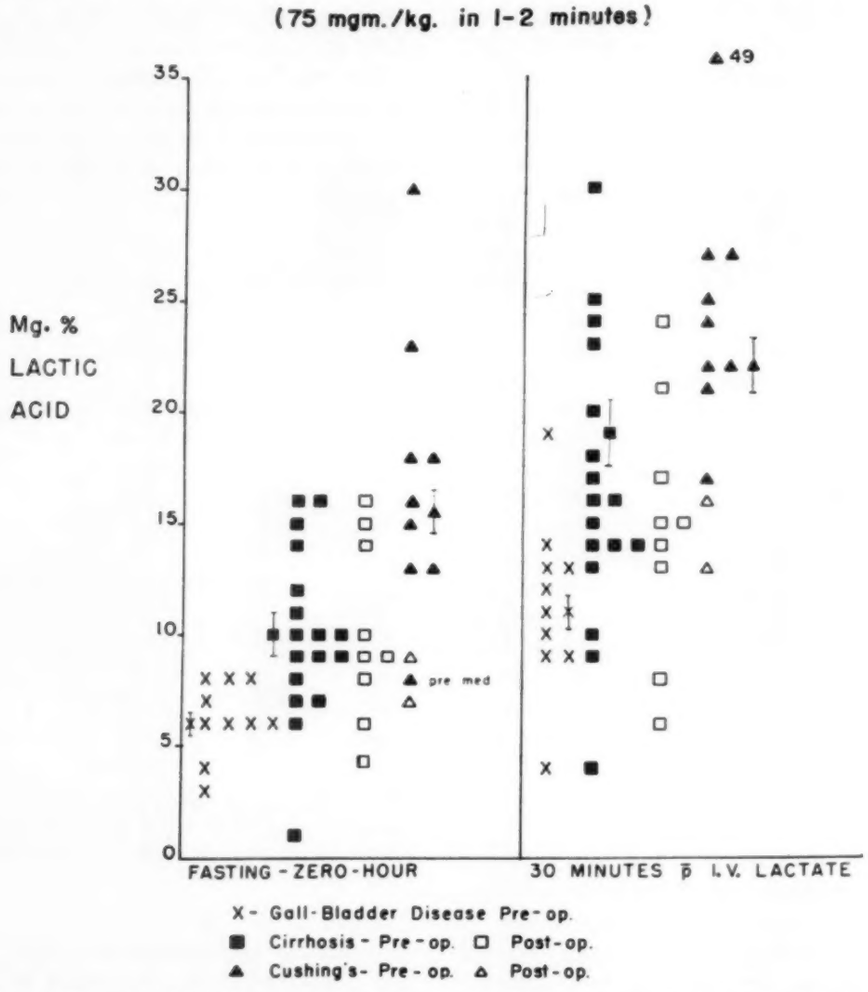

FIG. 4. Changes in blood lactic acid concentrations following the rapid intravenous infusion of sodium L (+) lactate. Mean concentrations and standard errors are shown for each group. One patient with Cushing's syndrome was tested following presurgery medication and is indicated by "pre med."

and pyruvic acid metabolism [*24–26*]. It is of interest that despite the evidence that cortisone treatment both decreases fat synthesis [*23*] and inhibits fat catabolism [*27*], we nonetheless observed a normal decrease in blood fatty acid and ketone concentrations following the administration of glucose. Alterations in lipid metabolism have been reported [*28*] but they are not constant. Our observed increase in cholesterol levels after the administration of glucose to patients with Cushing's syndrome is not understood; it is possible that this results indirectly from an alteration in insulin activity rather than from direct corticosteroid activity.

We believe our results are best explained by a direct effect of 17-hydroxycorticosteroids on glucose utilization. We suggest that these hormones inhibit the reaction

$$\text{Pyruvic acid} \xrightarrow[\text{CoA}]{\text{DPN}} \text{Acetyl-CoA} + CO_2 + \text{DPNH}$$

A decrease in pyruvic acid oxidation could account for the observed accumulations of lactic and pyruvic acid since lactic acid appears to be largely oxidized rather than repolymerized to glycogen [*29*]. This hypothesis is consistent with the observations of Villee, White and Hastings that in normal muscle the adrenal hormones favor the formation of lactate and decrease the oxidation of pyruvate [*30*].

The absence of alterations in citrate and

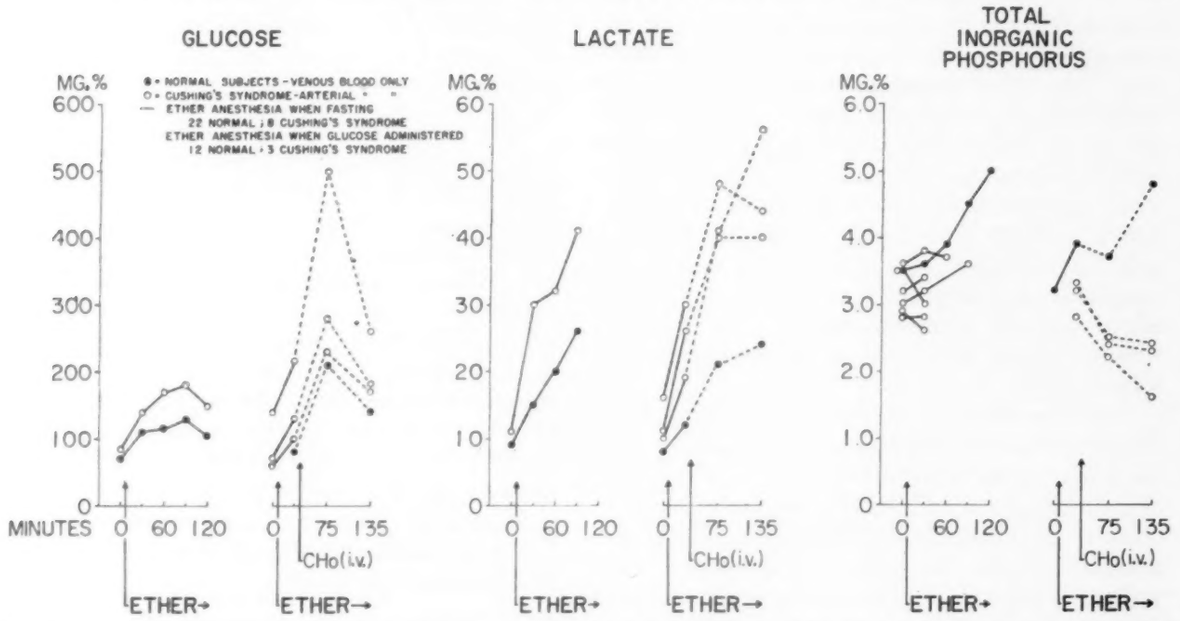

FIG. 5. Metabolic consequences of ether anesthesia when fasting and when glucose was administered in normal subjects and in patients with Cushing's syndrome. Only arterial blood was readily available under these conditions in the patients with Cushing's syndrome; concentrations of lactic and pyruvic acids are lower in arterial than in venous blood.

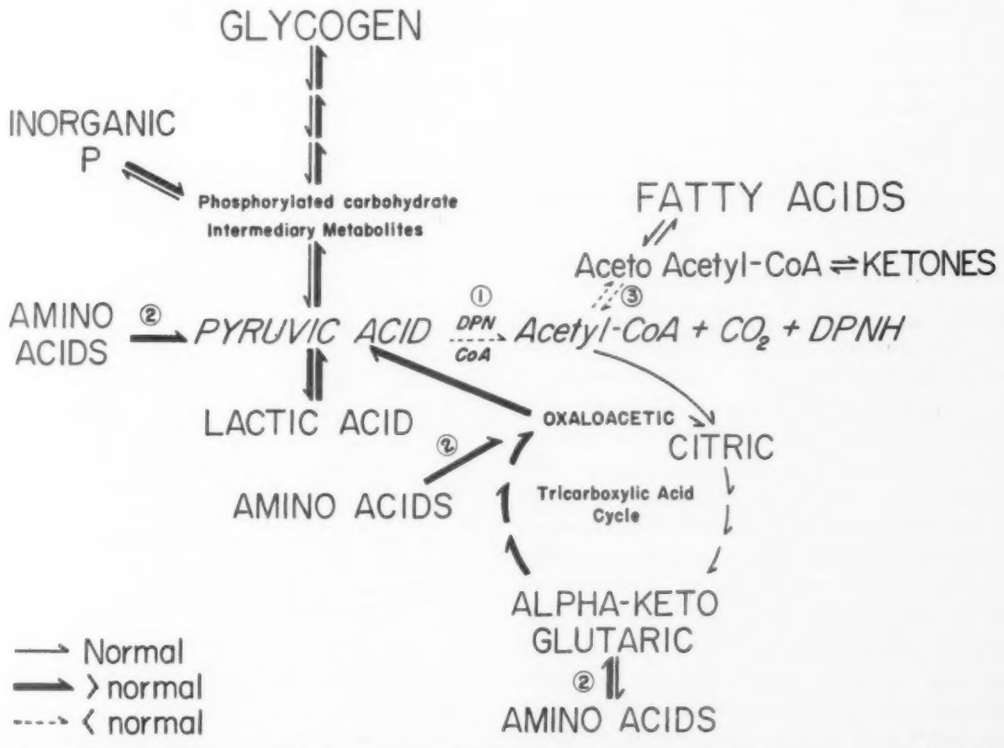

FIG. 6. Schematic representation of proposed site of direct action of 17-hydroxycorticosteroid hormones on carbohydrate metabolism. These hormones are believed to act at the level of reactions (1), (2) and (3): direct inhibition of pyruvate conversion to acetyl CoA as indicated by (1); increase in gluconeogenesis from protein at the steps indicated as (2); and decrease in fat catabolism and synthesis as indicated by (3).

alpha-ketoglutarate concentrations, the lack of ketosis and the normal changes in ketone and total fatty acid concentrations following the administration of glucose suggest that the tricarboxylic acid cycle is functioning in a normal manner. Substrate material for this oxidative cycle is provided by way of fatty acid oxidation and acetyl-CoA as well as by amino acid conversion to carbohydrate. The 17-hydroxycorticosteroids probably have a direct stimulatory effect on this gluconeogenesis from protein sources. Figure 6 demonstrates our hypothesis schematically.

The abnormalities in serum total inorganic phosphorus concentrations are not understood. Increased renal phosphorus excretion cannot explain the abnormalities in phosphorus metabolism when glucose is administered during ether anesthesia [*31*]. We suggest rather that they reflect a failure of phosphorylating reactions whereby intermediary carbohydrate metabolites are phosphorylated during glycolysis and oxidation: the postulated direct inhibition by adrenal hormones of the conversion of pyruvate to acetyl-CoA might initiate such a failure.

The observed accentuation by ether anesthesia of the abnormalities in patients with Cushing's syndrome suggests that the metabolic effects of ether itself are related to 17-hydroxycorticosteroid activity and hence to a decrease in pyruvate utilization [*32,33*]. However, they might result from a reflex release of epinephrine, as postulated by Brewster [*34*].

SUMMARY

Excessive accumulations of venous blood lactate and pyruvate, and decreased concentrations of serum total inorganic phosphorus have been observed in sixteen patients with confirmed Cushing's syndrome and in eleven patients on 17-hydroxycorticosteroid therapy. These abnormalities are observed following a high carbohydrate diet under conditions of (1) fasting, (2) glucose administration, (3) ether anesthesia when fasting and when glucose is administered, and (4) during the infusion of L (+) lactate. The differences in these patients from normal subjects and patients with mild to moderate diabetes mellitus are highly significant. Obese patients, with and without glucose intolerance, and patients with adrenal hyperplasia of other types do not demonstrate those abnormalities.

It is postulated that these changes reflect a direct inhibitory effect by 17-hydroxycorticosteroids on the oxidation of pyruvate to CO_2 and acetyl-CoA without any effect on the tricarboxylic acid cycle itself.

Acknowledgments: Patients were studied through the courtesy of the following physicians of the Massachusetts General Hospital: Drs. Fuller Albright, Philip H. Henneman, Anne P. Forbes, Robert Nielsen and Maurice Pechet; Drs. Oliver Cope and Benjamin Barnes; Drs. Reed Harwood, William McDermott, Leon Reznick and Harriet Hardy. The authors wish to thank Mrs. Amelia Yanakis, Mrs. Jean McLachlan and Miss Anne Murphy for their technical assistance and Dr. Claude Villee for his help and suggestions as our biochemical consultant.

Supported through the generosity of Mr. Edward Mallinckrodt and the Capps Fund, Harvard Medical School.

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Fructose and Diabetes*

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THE metabolism of fructose has engaged the attention of physicians since the systematic study of diabetes mellitus first began. In 1874 Eduard Külz [*32*] described in his monograph on diabetes experiments in which he had compared the effects of feeding fructose and other sugars to a group of diabetic patients. Ingestion of fructose was followed by a moderate reduction of glycosuria, and the author suggested that it be used in the dietary management of the disease. This observation received little attention until it was recalled by Minkowski [*44*] when in 1893 he reported his own experiments contrasting the effects of single oral doses of glucose and fructose in pancreatectomized dogs. When fructose was given, the amounts of sugar and nitrogen excreted in the urine decreased and the glycogen content of the liver increased.

This study, which was incidental to Minkowski's classic observations on the metabolic effects of pancreatectomy, stimulated widespread interest in the treatment of diabetes with fructose by mouth, and many experimental and clinical trials were reported in the succeeding years [*27–29,37,47,50*]. Fructose was usually given to patients either in a single dose in the morning or in divided doses with meals, the daily intake ranging up to 170 gm. [*27–29,47*]. On occasion, it produced a modest reduction of glycosuria and a rise in the respiratory quotient [*27–29,47*] but often [*37,47,50*] there was no appreciable metabolic change. It soon became apparent that superior utilization of fructose occurred only in patients with mild diabetes [*47*], and that even in these patients tolerance rapidly diminished with its continued use [*1,28,29,47,50*]. The employment of fructose in the management of diabetes quickly became unfashionable,‡ and by the time insulin was discovered in 1922 there was general agreement among physicians that its therapeutic value was very slight indeed. This conclusion stands as a curious background to the many modern studies which prove beyond any doubt that fructose is utilized normally, both by diabetic tissues *in vitro* [*3,12,36,56*] and by diabetic patients [*14,16,43,62*]. The present investigation focused upon this inconsistency in the hope that its resolution might illuminate certain facets of the diabetic state in man.

In designing observations on the metabolic effects of oral fructose, it seemed to us that its ineffectiveness in previous trials might be related to its being fed only once a day or at mealtimes. This meant that between meals the tissues had to be sustained by glucose synthesized in the liver from stored carbohydrate, fat or protein. We thought that if fructose were fed to the patient continuously, the interprandial synthesis of glucose might be inhibited and sustained utilization of fructose by the tissues might then become apparent. Consequently a synthetic liquid diet was prepared and delivered to the patient by pump through an indwelling gastric tube at a constant rate day and night. By this means, fructose was made the sole carbohydrate in the diet, and the interprandial fasting periods were abolished. As we had hoped, establishment of a stable absorptive state unmasked the ability of fructose to induce sharply defined changes in all aspects of metabolism in otherwise untreated diabetic patients.

PROCEDURE

Design of Experiment. Eight diabetic patients were selected for study in a metabolic unit. Their insulin was discontinued, and their diabetes was allowed to return to its uncorrected state. The milder cases stabilized; the more severe cases slowly deteriorated; and the very severe cases

‡ Osler urged its use in the second edition of his textbook (1895) [*51*] but omitted any reference in succeeding editions.

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rapidly passed into acute diabetic acidosis. Except for the latter, in whom prolonged observations were impossible, the study was divided into four periods. For the first few days the patient consumed a three-meal-per-day solid diet, isocaloric with the liquid tube feeding which was to follow. During this preliminary phase fasting blood samples were obtained early each morning. Next came the "pretherapy control period." A nutritionally balanced synthetic liquid mixture containing glucose as the sole carbohydrate was delivered by tube into the gastrointestinal tract at a constant slow rate around the clock. Blood was collected each morning as before; these were of course no longer fasting samples. During the "therapy period" the liquid diet was identical in rate of delivery and in composition except that the glucose was entirely replaced by an isometric amount of fructose. Finally, in the "post-therapy period" glucose was given once more. By this technic it was possible to compare the metabolic effects of fructose and glucose under stable and constant conditions.

Most patients tolerated the tube feeding remarkably well for days or weeks despite the obvious inconveniences involved. The fine transnasal polythene catheter occasioned little discomfort, and the delivery tube was long enough to permit considerable freedom of activity within the ward. The chief complaint was that of periodic hunger, which was only partially controlled by the high caloric intake. Water was generally allowed *ad libitum* because of the glucose diuresis. In cases in which withdrawal of caffeine caused distress (not an uncommon event), three or four cups of black coffee were permitted throughout the day. From the point of view of the investigator, the technic of continuous tube feeding obviated many of the usual problems of metabolic balance studies. The mixture was easily prepared, its composition precisely known, its delivery constant, and its absorption complete.

Diet. The liquid synthetic diet was balanced and nutritionally adequate in all respects. It consisted of a solution in distilled water of amino acids (amigen,® Mead Johnson), emulsified fat (carbohydrate-free lipomul,® Upjohn; 36 per cent peanut oil, 4 per cent coconut oil), crystalline glucose or fructose, minerals and vitamins. The caloric value was set at the basal caloric requirement plus 80 per cent; 13 per cent of calories were from protein, 30 per cent from fat, and the remainder from carbohydrate. The mineral content, based on average normal daily intake, differed somewhat for different patients. Usually it was exactly 4.7 gm. potassium (120 mEq.), 5.6 gm. sodium (245 mEq.), 7.8 gm. chloride (220 mEq.), 0.45 gm. magnesium, 1.75 gm. calcium, and 1.65 gm. phosphorus. Water- and fat-soluble vitamins (poly-vi-sol,® Mead Johnson; 1 ml./24 hours) were added in excess of the daily amounts recommended by the Nutrition Board of the National Research Council. The mixture was made up fresh every day and kept on ice at the bedside to avoid bacterial spoilage and resultant diarrhea.

Methods of Analysis. Measurements were made of glucose, fructose, acetone, lactate, pyruvate, sodium, potassium, phosphorus and nitrogen. True glucose values were obtained by the method of Somogyi and Nelson [*48,63*]. Fructose was measured by the diphenylamine reaction according to the method of Kendrick [*30*]. Total acetone (acetone plus beta-hydroxybutyric acid and aceto-acetic acid expressed as acetone) was measured by the method of Michaels et al. [*42*] as modified by Sargent [*60*]. Blood lactic acid was measured by the method of Barker and Summerson [*4*]. Blood pyruvic acid was measured by the method of Friedemann and Haugen [*19*], employing extraction with ethyl acetate and 10 per cent sodium carbonate. Inorganic phosphate was measured by the method of Gomori [*22*] as modified by Power [*53*]. Sodium and potassium estimations were made in the conventional manner with the Beckman flame photometer. Food and urine nitrogen was measured by the micro-Kjeldahl method of Keys [*31*].

Subjects. Eight diabetic patients and one healthy non-diabetic subject were studied. On clinical grounds the diabetic patients belonged to the adult, non-obese, stable, insulin-responsive group. When their insulin was discontinued, all but one lost weight. The grouping of the cases according to the severity of the diabetes is shown in Table 1 and was based upon the level of the fasting blood glucose during the initial period of the study.

RESULTS

The continuous feeding of fructose produced a well defined improvement in all save the most severely diabetic patients. In general, the degree of improvement varied inversely with the severity of the diabetes as defined by the height of the fasting blood glucose level without insulin. In

TABLE 1

SUMMARY OF CLINICAL DATA FROM DIABETIC PATIENTS STUDIED BY THE TECHNIC OF CONTINUOUS TUBE FEEDING WITH A SYNTHETIC DIET CONTAINING FRUCTOSE AS THE SOLE CARBOHYDRATE *

Patient	Sex and Age (yr.)	Age When Diabetes Diagnosed	Weight (lb.)	Daily Insulin Dosage (units)	Fasting Blood Glucose (mg./100 ml.)	Severity of Diabetes
F. H.	M, 50	..	176	0	80	Non-diabetic control
M. M.	F, 28	28	87	0	150	Mild to moderate
M. E.	M, 58	55	172	0	150	Mild to moderate
A. S.	M, 57	55	170	20	170	Mild to moderate
C. M.	M, 61	57	158	40	240	Mild to moderate
M. J.	F, 68	54	123	50	450	Moderately severe
A. G.	F, 59	47	105	60	450+	Severe
M. S.	F, 42	36	97	60	950	Severe
S. T.	M, 39	34	156	120	700+	Severe

* The patients are grouped according to the severity of their diabetes as defined by the height of the fasting blood glucose level after stopping injections of insulin. With the exception of patient M. E., weight loss and ketosis developed in all patients.

keeping with this was the observation that while fructose was administered the blood glucose remained at, but never below, the fasting level which had been established in the preliminary phase of the study. Improvement of the diabetes was manifested by a reduction of blood glucose levels and lessening or disappearance of glycosuria, a decline in the production and excretion of acetone, a decrease in the loss of water, electrolytes and nitrogen in the urine, and a gain in body weight. In no instance—from the healthy subject to the most severely diabetic patient—was fructose recovered from venous or arterial blood, or from the urine. Its absence from arterial blood implies that all the dietary fructose was assimilated by the splanchnic system* and that none reached the periphery.† If this is true, the liver was the site of all the metabolic changes observed. Emphasis is again directed toward the fact that in these diabetic patients all the metabolic alterations toward normality occurred entirely without the use of insulin; they were induced simply by the substitution of isometric amounts of fructose for glucose in the tube feeding.

Metabolic charts from the healthy subject and from four representative diabetic patients have been selected for presentation. In addition to the data shown on the charts, blood lactate, blood pyruvate, serum sodium, serum potassium, serum phosphorus and urinary sodium were measured throughout the experiments. These moieties did not show significant changes and have therefore been omitted for the sake of brevity. Alterations in urinary volume were generally related to its glucose content, and these also have been omitted.

CASE REPORTS

CASE 1. F. H., a fifty year old healthy laborer weighing 176 pounds, had no family history of diabetes and had a normal glucose tolerance curve. Figure 1 shows the changes in blood glucose levels throughout the experiment; the other moieties which were measured did not change significantly.

* Before reaching the arterial needle, the blood had of course traversed the lungs, which in perfusion experiments are capable of assimilating fructose [*66*].

† Unfortunately we could not prove beyond any doubt that fructose was completely absent from the peripheral blood. The technic used for the estimation of fructose was rendered somewhat insensitive by the presence of high concentrations of glucose. Appropriate recovery experiments indicated that levels of fructose below 3 to 4 mg. per 100 ml. might have been undetected. However, considering the slow rate of feeding (in the range of 0.25 gm. per minute) and the known affinity of the liver for fructose [*6,14,36,41,66*], it is reasonable to assume that the splanchnic system did take up all the ingested fructose. Furthermore, since the peripheral tissues utilize fructose poorly in the presence of glucose [*6,39,61,73*], traces of fructose in the blood, even if present, would not be likely to affect peripheral metabolism.

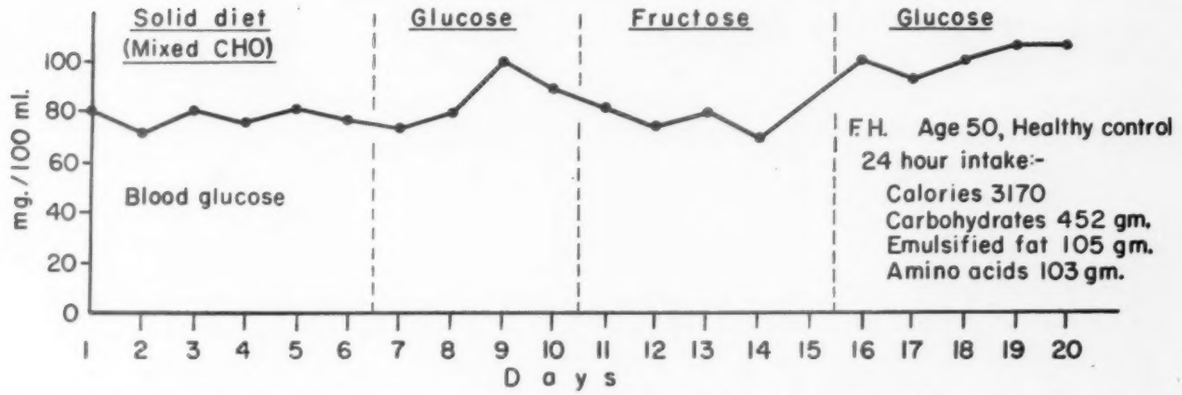

FIG. 1. Daily blood glucose levels from patient F. H., a healthy non-diabetic laborer. The abscissae represent time in days and the ordinates blood glucose in mg. per 100 ml. The interrupted vertical lines separate the periods during which the patient received a normal solid diet, continuous tube feeding containing glucose, and continuous tube feeding containing fructose. During fructose feeding the blood glucose values remained at the fasting level as determined in the initial period of the study. During glucose feeding the blood glucose level increased slightly even in this non-diabetic person. The increase is most marked in the final period, perhaps due to the previous absence of glucose from the diet.

Comment: In this and in each of the following studies 8:00 A.M. fasting blood samples were collected during the preliminary period of study while the patient was consuming an ordinary three-meal-per-day solid diet. The blood samples drawn each morning during the period of continuous tube feeding were, of course, not fasting. Even in this non-diabetic subject the content of glucose in the blood increased slightly during glucose feeding whereas during fructose feeding the value remained at the fasting level. The elevation of the blood glucose level was most marked in the final period when glucose replaced fructose in the diet. This may represent an impaired tolerance for glucose due to its previous absence from the diet for five days [*24*].

CASE II. M. E., a fifty-eight year old railway man weighing 170 pounds, had mild, asymptomatic, untreated diabetes of three years' duration. During the preliminary study period, when he was consuming a solid diet, his 8:00 A.M. fasting blood glucose level was found to be 150 mg. per 100 ml. During tube feeding with glucose in the mixture, the 8:00 A.M. blood glucose rose to a level of 275 mg. per 100 ml. When fructose was substituted for glucose the blood glucose values returned to the fasting level. At the same time the amount of glucose in the urine decreased from 100 gm. per day to 5 or 10 gm. per day, and the excretion of potassium sharply diminished. The amounts of these substances in the urine and blood quickly increased to their previous levels when feeding with glucose was resumed. At no time was there significant ketosis. The excretion of inorganic phosphate and nitrogen did not change; nitrogen balance was positive throughout the study. The body weight remained constant. (Figs. 2 and 3.)

Comment: In this patient with mild diabetes, fat and protein metabolism were not disturbed. The metabolic change during fructose feeding was confined to improved assimilation of carbohydrate, as shown by the restoration of blood glucose to the fasting level, the sharp reduction of glycosuria and the retention of potassium. Figure 3 illustrates that the glucose content of the blood diminished very soon after glucose in the diet was replaced with fructose.

CASE III. C. M., a sixty-one year old photographer weighing 155 pounds, had moderate diabetes of four years' duration. This had been well controlled with 40 units of NPH insulin per day. While consuming the solid diet during the preliminary period of study, the 8:00 A.M. fasting blood glucose level was 240 mg. per 100 ml.; glycosuria was in the range of 30 gm. per day, and the blood acetone level was 15 mg. per 100 ml. When tube feeding containing glucose was instituted, the blood glucose level increased to 390 mg. per 100 ml. and glycosuria reached 115 gm. per day. When fructose was substituted for glucose in the feeding mixture, the blood glucose returned to its fasting level, glycosuria ceased, phosphate and potassium excretion declined precipitously, the blood acetone content was reduced from 15 to 4 mg. per 100 ml. and nitrogen balance became strongly positive. In order to determine the constancy of this improvement in the diabetic state, continuous fructose feeding was maintained for three weeks. Not only did the improved status continue, as shown by the laboratory tests, but during this time the patient gained 10 pounds in body weight. (Fig. 4.)

Comment: The data from this case of moderate diabetes best exemplify the restoration of carbohydrate, fat and protein utilization to or toward normal by the constant ingestion of fructose. The effects were maintained as long as fructose was continued. The study could not be completed by the final substitution of glucose for fructose as the patient, quite reasonably,

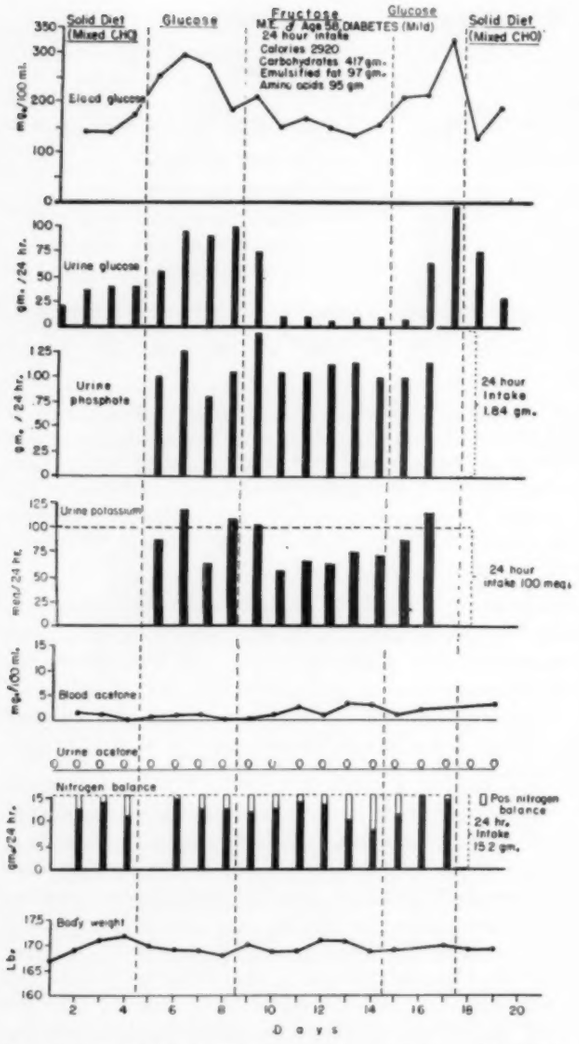

FIG. 2. Metabolic data from patient M. E. with mild diabetes mellitus. The ordinates represent blood or urine levels of the various metabolites which were measured. The abscissae represent time in days. The interrupted vertical lines separate the periods during which the patient was given a normal solid diet, continuous tube feeding containing glucose, and continuous tube feeding containing fructose. The fasting blood glucose level, determined in the preliminary period, was 150 mg. per 100 ml. During tube feeding with glucose in the mixture the blood glucose level increased to 275 mg. per 100 ml. and glycosuria increased to 100 gm. per day. When fructose was substituted for glucose the blood glucose returned to the fasting level. The amount of glucose in the urine decreased to 5 or 10 gm. per day and the excretion of potassium sharply diminished. These values once again increased when feeding with glucose was resumed. Blood acetone levels were not elevated; the excretion of inorganic phosphate and nitrogen did not change and the body weight remained constant.

demanded solid food at the end of twenty-five days of tube feeding.

CASE IV. M. J., a sixty-eight year old grandmother weighing 123 pounds, had moderately severe diabetes of fourteen years' duration which had been well controlled with 50 units of NPH insulin per day. While consuming a solid diet the 8:00 A.M. fasting blood glucose level was found to be 400 mg. per 100 ml., 200

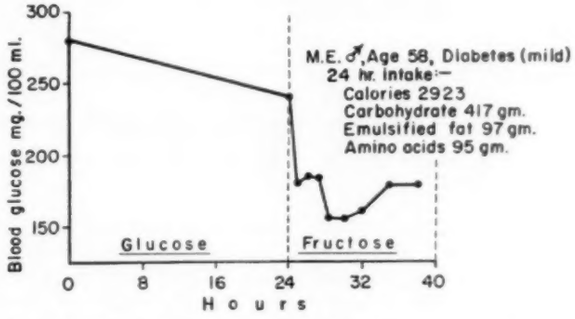

FIG. 3. Blood glucose levels during forty hours of continuous tube feeding, from patient M. E. with mild diebetes mellitus. During the time indicated by the interrupted vertical lines, the tube feeding contained fructose in place of glucose as the sole source of carbohydrate. Note the decrease in the blood glucose level which occurred within forty-five minutes after the change was made.

gm. of glucose were excreted in the urine each day, and the blood acetone content was in the range of 5 to 8 mg. per 100 ml. When she was given tube feeding containing glucose, the blood glucose level increased to around 550 mg. per 100 ml. and glycosuria increased to 350 gm. per 24 hours. When fructose was given in place of glucose, the blood glucose returned to the fasting level, glycosuria diminished to around 250 gm. per 24 hours, and phosphate excretion decreased appreciably. Potassium excretion changed little, if at all. The levels of acetone in blood and urine diminished slightly, and nitrogen balance tended to improve. Body weight, which had been falling rapidly, stabilized and even rose a little. All these parameters deteriorated again when feeding with glucose was resumed. (Fig. 5.)

Comment: The data from this patient, whose diabetes was considerably more severe than that of the previous two cases, show a well defined but less marked response to continuous fructose feeding. Carbohydrate retention improved but in spite of complete assimilation of the fructose in the diet, ketosis, nitrogen balance and weight loss responded only slightly.

CASE V. S. T., a thirty-nine year old shopkeeper weighing 150 pounds, had severe diabetes of five years' duration which required up to 120 units of NPH insulin daily for control. Profound diabetic acidosis developed so rapidly when insulin was withheld that a prolonged metabolic balance study was quite impossible. Therefore the rate of development of hyperglycemia and ketosis during fructose feeding was simply compared with that which occurred during

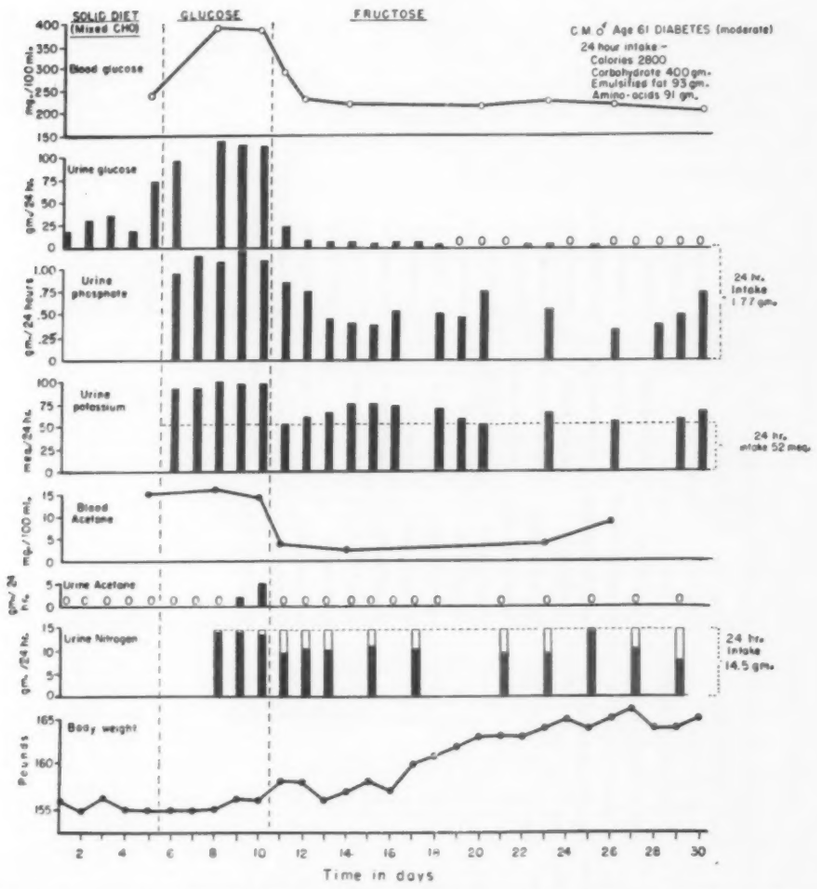

FIG. 4. Metabolic data from patient C. M. with moderate diabetes mellitus. The conventions of the diagram are the same as for Figure 2. The fasting blood glucose level shown in the initial period was 240 mg. per 100 ml. and the blood acetone level was 15 mg. per 100 ml. During tube feeding with glucose the blood glucose level increased to 390 mg. per 100 ml. and glycosuria increased to 115 gm. per day. When feeding with fructose was instituted, the blood glucose returned to the fasting level, glycosuria ceased, phosphate and potassium excretion sharply diminished, the blood acetone level decreased to 4 mg. per 100 ml., nitrogen balance became strongly positive, and there was a gain of 10 pounds in body weight over a three-week period.

feeding with glucose. Eighteen hours before the beginning of the observation shown in Figure 6, tube feeding was started and the last dose of NPH insulin was given. It can be seen that glucose and acetone levels in the blood increased at the same rate regardless of the dietary carbohydrate. Within thirty-six hours the blood glucose reached 700 mg. per 100 ml., and the blood acetone, 30 mg. per 100 ml. During each thirty-six-hour period the patient excreted 11 L. of water, 500 gm. of glucose and 35 gm. of acetone. In spite of the enormous carbohydrate loss, no fructose was recovered from blood or urine.

Comment: This patient is representative of the three severely diabetic patients who were studied. They derived no measurable improvement in their diabetes from the assimilation of fructose.

CASE V (cont'd.). Figure 7 describes the results of an experiment to determine whether the ineffectiveness of feeding fructose to the severely diabetic patients was a manifestation of a qualitative or simply a quantitative difference in the nature of their diabetes. This was studied in patient S. T. by a brief observation of his metabolic balance while his diabetes was partially controlled with 50 units of NPH insulin per day. For one week he was fed with a tube feeding containing fructose, and then for five days with a tube feeding containing glucose. During the latter period the blood glucose level increased from 300 ot 400 mg. per 100 ml. to 600 mg. per 100 ml.; glucose excreted in the urine increased from less than 100 gm. per day to 300 gm. per day; nitrogen excretion increased sharply; and the body weight decreased. Phosphate, potassium and acetone levels were not altered.

Comment: While not conclusively established by this experiment, it seems likely that the failure of fructose to influence severe diabetes is related to the extent of the metabolic derangement and not to any qualitative

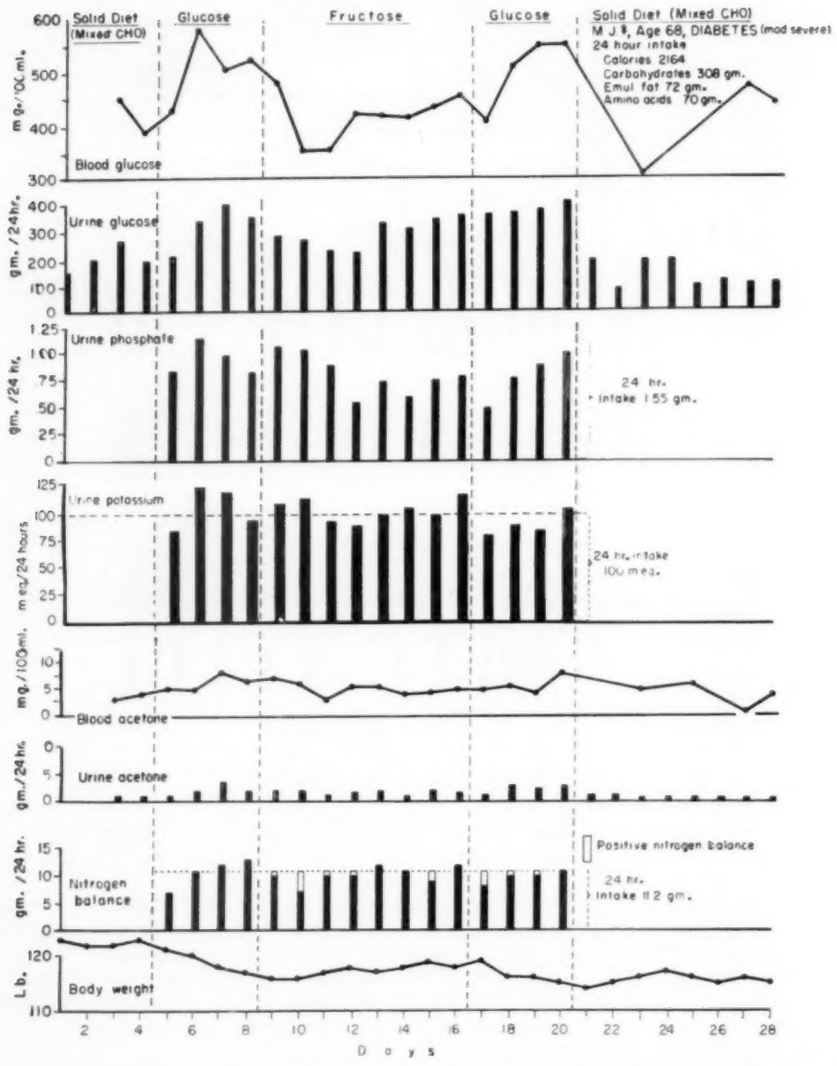

FIG. 5. Metabolic data from patient M. J. who had moderately severe diabetes mellitus. The conventions of the diagram are as for Figure 2. The fasting blood glucose level while the patient was consuming a solid diet was 400 mg. per 100 ml. When she was given tube feeding containing glucose, the blood glucose level increased to about 550 mg. per 100 ml. and glycosuria reached 350 gm. per twenty-four hours. When fructose replaced glucose in the tube feeding, the blood glucose returned to the fasting level, glycosuria diminished to about 250 gm. per twenty-four hours, and phosphate excretion diminished slightly. Potassium excretion did not change. The levels of acetone in blood and urine diminished slightly, nitrogen balance improved somewhat; and the body weight stabilized. These improvements ceased when feeding with glucose was resumed.

metabolic difference between the patients with severe diabetes and the milder cases.

COMMENTS

In modern times investigation of the effects of fructose by mouth has been unpopular because of uncertainty surrounding the extent of its conversion to glucose during intestinal absorption. Under certain experimental conditions this may take place at a fairly rapid rate [*6,74*] but under natural circumstances it probably does not. Normal intact rats receiving fructose by continuous tube feeding exhibited high levels of fructose in the portal blood without increase in its glucose content [*24*]. Our opinion that conversion of fructose to glucose in the intestine during the present studies would not be of quantitative importance was borne out by the experimental results. These clearly show that continuous fructose feeding had a well defined effect on metabolism in diabetes. Not only was carbohydrate utilization improved, but ketosis

was diminished and nitrogen balance was restored. It was also apparent that correction of the metabolic lesions was not always complete and that in general the degree of improvement varied inversely with the severity of the diabetes as defined by the fasting blood glucose level.

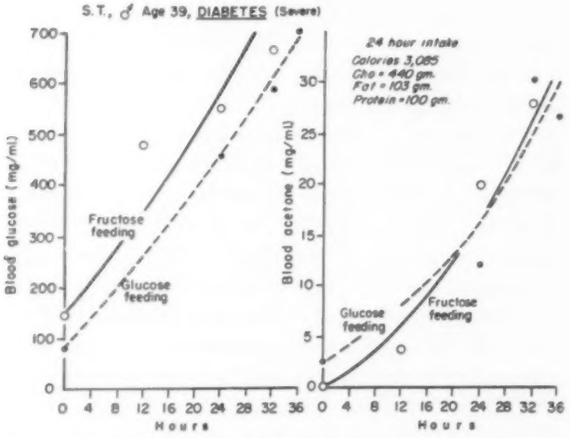

FIG. 6. Blood glucose and acetone levels from patient S. T. who had severe diabetes mellitus. The abscissae represent time in hours. The left hand figure represents blood glucose levels on each of two separate days; in one case during tube feeding with glucose in the mixture (interrupted line) and in the other case during tube feeding with fructose in the mixture (solid line). The right hand figure represents blood acetone levels during the same two experiments. In each case eighteen hours before the beginning of the measurements shown here tube feeding was started and the last dose of NPH insulin was given. Note that in this severely diabetic patient blood glucose and acetone levels increased at the same rate, irrespective of the carbohydrate in the diet.

When this was high, acetonemia and nitrogen loss continued unabated, despite continuous ingestion of fructose.

Metabolic Abnormalities in Diabetes Mellitus. Modern concepts of diabetic physiology at the organ and cellular level are derived largely from the study of experimental insulin deficiency induced in animals by chemical or surgical extirpation of the pancreatic beta cells. It is unlikely that hyperglycemia in the human being is always caused by insufficient insulin, or that the clinical syndrome of diabetes mellitus is a single disease entity [*8*]. With a single exception the present studies were performed upon weight-losing, potentially ketotic patients.

Figure 8 represents current views on intracellular metabolic pathways and the chief abnormalities which exist in animal diabetes caused by insulin deficiency. Lack of insulin interposes a block between glucose and glucose-6-phosphate, the other steps in the Embden-Meyerhoff cycle being intact [*12*]. The original view [*13*] that insulin catalyses the hexokinase system has been found untenable [*9,52,65*]. Levine has shown that insulin exerts control over glucose phosphorylation by facilitat-

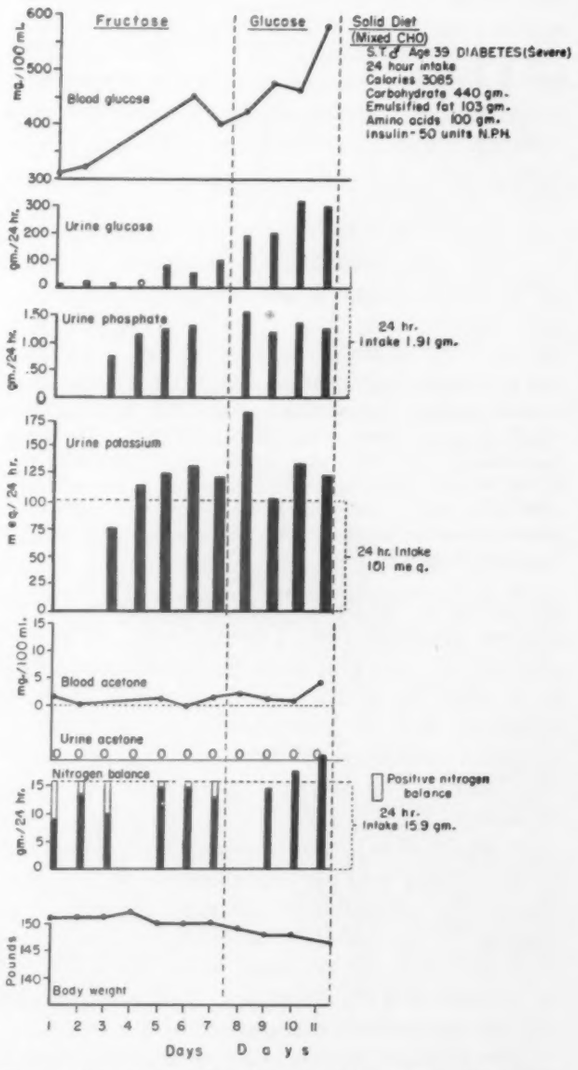

FIG. 7. Metabolic data from patient S. T. with severe diabetes mellitus (the same patient as in Figure 6). Throughout this experiment he was given 50 units of NPH insulin at 8:00 A.M. each day. The conventions of the diagram are as for Figure 2. After tube feeding with a mixture containing fructose for one week, he was given a mixture containing glucose for five days. During the latter period the blood glucose level increased from 300 or 400 mg. per 100 ml. to 600 mg. per 100 ml., glycosuria increased from less than 100 gm. per day to 300 gm. per day, nitrogen excretion increased sharply, and the body weight decreased. Electrolyte and acetone levels did not change.

ing the transfer of glucose from the extracellular fluid across the cell membrane into the cell [*35*], and his observation has been proved correct by a number of technics [*52,59*]. The action of insulin on the membrane transfer system is a specific catalytic effect and is related to the spatial con-

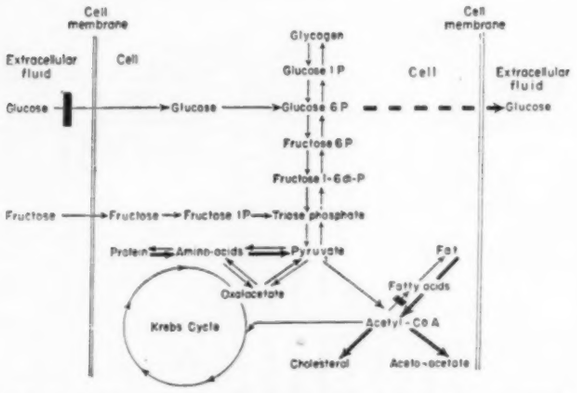

FIG. 8. A highly diagrammatic representation of the chief steps in intracellular metabolism and the abnormalities which occur in experimental diabetes mellitus. The solid bars indicate pathways that are blocked in diabetes; the heavy arrows, pathways which proceed at an excessive rate. The site of entry of fructose into the scheme is based upon the work of Hers and Kusaka [*23*] and of Leuthart et al. [*34*].

figuration of the first three carbon atoms of the glucose molecule [*20*]. The diabetic cell is impermeable to the glucose in the fluid surrounding it, so that the activity of its glycolytic cycle is impaired due to insufficiency of substrate, a situation analogous to that occurring in starvation [*38,75*]. The present experiments and those of others [*3,26,45*] suggest that this cellular glucose deprivation is the stimulus which causes the liver to bring into play mechanisms for adaptation to starvation despite the superabundance of glucose in the blood: gluconeogenesis increases [*2,55,56,68,71*]; the synthesis of fat [*10,11,68*] and of protein [*18,25*] decreases; and acetate and related compounds accumulate in the blood.

The cellular permeability of fructose, which has a different molecular configuration from that of glucose, is not insulin-dependent [*20*]. The high affinity of the normal liver for fructose [*41,66*] is not lost in the diabetic state. Diabetic liver slices utilize fructose at a normal rate [*12,56*] as does the intact organ [*14,36*].*

* Studies on fructose utilization by diabetic muscle are lacking, nor is the status of normal muscle clear in this regard. In general, hindlimb perfusion experiments [*40, 66*] and measurement of arteriovenous differences [*69*] have suggested good utilization of fructose by muscle, whereas eviscerated animals [*6,73*] have exhibited only slight fructose utilization. It may be surmised that these inconsistencies are related to inhibition of fructose utilization by the presence of glucose [*39,61*]. Fructose is utilized scarcely at all by brain [*6,61*].

Fructose therefore is not subject to a block at the cell membrane in the presence of insulin deficiency. It can enter freely into the glycolytic cycle whence it may be utilized to provide energy, or is laid down as glycogen, or transformed to fatty acids and other compounds. These facts provide the theoretic basis for the present experiments, for by providing a continuous supply of fructose it was possible to restore metabolism—at least in the liver—without supplying exogenous insulin.*

The Effects of Continuous Fructose Feeding. The small concentrations of fructose constantly being absorbed into the portal blood under the conditions of these experiments were apparently completely removed in passage through the liver. Fructose was not present in arterial or venous blood or in the urine. Therefore although fructose was the only carbohydrate in the diet, glucose was the only carbohydrate delivered to the peripheral tissues. Metabolic fragments of fructose may have reached the periphery at an increased rate but this was not reflected by an increase in the pyruvic or lactic acid content of the blood. From these observations follows the conclusion that the effects of continuous fructose feeding upon metabolism in diabetes take place entirely within the liver, and the suggestion that in diabetes the liver may be the site of the major metabolic abnormalities.

The original hypothesis upon which these experiments were based, namely, that abolishing periods of fasting by continuous feeding of

* Concepts of glucose homeostasis and of the diabetic state will need considerable revision in the future, judging from fragmentary evidence available at the present time. With one exception [*54*] recent experiments suggest that hepatic metabolism is not directly under insulin control. Insulin promptly increases glucose uptake by muscle but it has no effect on glucose uptake by isolated liver *in vitro* [*57*] or by perfusion [*49*]. It must be given to the intact animal for several hours before the liver is removed for an effect on hepatic metabolism to be manifest [*57*]. There is no published information as to the permeability of the liver cells to glucose in the presence and absence of insulin; all experiments on permeability have been done on isolated muscle [*52*], the optic lens [*59*] or eviscerated animals [*35*]. Some as yet unknown humoral substance, not insulin, may regulate glucose uptake and utilization by the liver. It is of interest in this regard that the release of a humoral glucose-regulating substance by exercising muscle has been clearly established [*21*].

fructose would inhibit gluconeogenesis, proved to be incorrect. During feeding with fructose the blood glucose behaved as though the patient were fasting. This is in keeping with the observation that the hormonal glucostatic mechanisms of the body do not respond to fructose [*70*]. Fructose is in this sense an inert sugar which is removed from the blood by the liver without affecting or being affected by the endocrine balance. In the liver, fructose entered all the metabolic channels normally open to glucose. In the complete absence of exogenous insulin it restored to or toward normal the storage of carbohydrate [*67*], the overproduction of ketone bodies, the wastage of nitrogen and the loss of weight. The findings confirm and extend observations which have been made in animal experiments [*3,26,44,45*]. Minkowski [*44*] observed long ago that pancreatectomized dogs excreted less nitrogen in the urine when they were fed fructose. Diets containing fructose restored hepatic fatty acid synthesis [*3*] and inhibited hepatic cholesterol synthesis [*26*] in otherwise untreated alloxanized rats. Glucose itself in high concentration was antiketogenic in pancreatectomized dogs [*45*]. These findings, together with our own, strongly suggest that insulin deficiency *per se* causes but a single metabolic fault: impairment of cellular permeability to glucose. The other metabolic aberrations occurring in ketotic, protein-wasting diabetic patients appear to result not directly from lack of insulin, but rather to be normal, albeit exaggerated, responses to the stimulus of hepatocellular carbohydrate depletion.

Finally, it is necessary to explain the ineffectiveness of continuous fructose feeding in patients with severe diabetes characterized by high fasting blood glucose levels and intense glycosuria. It was not due to any inability to assimilate fructose. The large quantities of sugar found in blood and in urine consisted entirely of glucose, even though fructose was the only carbohydrate in the diet. The only possible source of this glucose was the liver; clearly then, the liver must have been synthesizing and releasing glucose at an abnormally rapid rate. It seems probable that glucose was escaping from the hepatic cells as fast as fructose entered them, that there was, therefore, no net gain in intracellular carbohydrate, and that this was the reason why acetonemia and negative nitrogen balance continued unabated. The present experiments indicate that continued accelerated hepatic glucose release, which must exist in all patients with diabetes severe enough to cause intense glycosuria during fasting, is a hepatocellular derangement distinct from, and perhaps quite as important as, the defect in glucose uptake [*64*]. It has been confirmed, both *in vitro* [*55,56*] and *in vivo* [*71*], that hepatic glucose production is increased in diabetes,* and recent studies have shown that glucose-6-phosphatase activity is accelerated in diabetic liver [*2,33*]. Glucose-6-phosphatase commands the "final common pathway" of glucose release. It is affected only indirectly by insulin and adrenocorticoids [*2*]; direct regulating mechanisms are quite unknown. This lack of knowledge of the factors governing the "exit side" of the liver cell poses a serious gap in our understanding of glucose homeostasis.

The Use of Fructose in the Treatment of Diabetes in Man. The apparent inconsistency between the ineffectiveness of feeding fructose to diabetic patients, as practiced before the discovery of insulin, and the normal utilization of fructose in diabetes, as shown by more recent experiments, would seem to be adequately resolved by the present studies. There are at least two reasons why oral fructose is not a useful therapeutic agent: (1) Practical usage necessitates periodic feedings. These do not provide a continuous flow of substrate to the hepatic glycolytic cycle, which is the mechanism by which fructose is thought to exert its effect. (2) The diabetic liver exhibits a defect in the control of glucose release as well as a defect in the control of glucose uptake. Fructose overcomes only the latter. The same arguments apply to the use of intravenous fructose. Furthermore, whatever its theoretic advantages [*16,17, 43,58*], from a practical point of view intravenous glucose and insulin are safer and just as effective. Fructose obscures the laboratory picture, leads to unexpected hypoglycemic reactions, and does not hasten recovery from ketosis [*46*].

SUMMARY

The metabolic effects of fructose have been studied in one healthy subject and in eight diabetic patients by observing their metabolic balance while feeding them continuously with a synthetic liquid diet containing fructose as the sole carbohydrate. In each case treatment with insulin was stopped. The mixture was pumped through a tube into the gastrointestinal tract at a

* The contrary or equivocal results found by the hepatic vein catheterization technic [*5,7,15*] may be surmised to be due to the nature of the cases studied.

slow, constant rate around the clock. Fructose given in this way was completely utilized or stored; none was recovered from the blood or the urine. During continuous feeding with fructose the blood glucose in each patient stabilized at his own particular fasting level, never below it. Glycosuria diminished, or disappeared if the fasting level was below the renal threshold. Coincidentally with the improved utilization of carbohydrate, potassium and phosphate were retained in considerable amounts.

By continuously providing a carbohydrate such as fructose which can be utilized without insulin by the patient with diabetes, it was possible in the milder cases to correct or improve the overproduction of acetone, the negative nitrogen balance and the loss of weight, in the complete absence of exogenous insulin. Since no fructose was present in the peripheral blood its effects apparently originated within the liver. These findings confirm and extend those of others in animal experiments, and strongly suggest that the abnormalities of fat and protein metabolism in diabetes are not due to lack of insulin *per se* but are caused by the impairment of normal utilization of carbohydrate which occurs with insulin deficiency.

Fructose was not effective in severe diabetes characterized by high fasting blood glucose levels, intense glycosuria and rapid onset of severe ketosis. Reasons are given for attributing the ineffectiveness of fructose in these patients to an accelerated rate of hepatic glucose release, so that no gain in the amount of carbohydrate available within the liver cell can occur. Knowledge of the mechanisms governing the rate of release of glucose from the liver cells is fragmentary.

It is our opinion that the therapeutic usefulness of fructose is slight. Its continuous or very frequent administration is not practical under ordinary circumstances. Of greater importance is the fact that while it bypasses the defect in hepatic glucose uptake, it does not inhibit the accelerated rate of hepatic glucose release. In the severely diabetic patient the latter appears to be a significant metabolic lesion.

Acknowledgments: Grateful acknowledgment is made to the following persons for their help during this study: Dr. Robert C. Little, Director of Clinical Research, Mead Johnson and Company, for generous supplies of crystalline fructose and amigen; Dr. Edward A. Hawk, Department of Clinical Investigation, The Upjohn Company, for generous supplies of carbohydrate-free lipomul; Miss Dolores Rix, Mrs. Mary Lou Bowers, and Mrs. Ella Fields for technical assistance; the late Mrs. Florence M. Ross and Miss Rosemary Gleason for planning and preparing metabolic diets, and Miss Loretta Cudnowski, nurse in charge of the metabolic unit.

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The Management of Hepatic Coma in Relation to Protein Withdrawal and Certain Specific Measures*

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PROGRESSIVE liver disease of any etiology may culminate in hepatic coma and the grave prognosis of this complication is generally accepted. Recent contributions to the symptomatology and metabolic basis of hepatic coma have led to the introduction of new methods of treatment which demand critical appraisal as results are often equivocal. Interest in therapy was stimulated by the demonstration of a relationship between the neuropsychiatric disorder and toxic nitrogenous substances derived from the intestines. The characteristic syndrome and electroencephalogram changes [*1*] can be induced in some patients with liver disease by dietary protein and certain other nitrogenous substances given orally [*2,3*]. Identical changes may occur spontaneously in a chronic form in patients with extensive portal collateral circulations [*4*] or following portacaval anastomosis [*5*] and amelioration follows reduction of protein intake. No specific nitrogenous metabolite has been incriminated beyond dispute but ammonia, which can reach the nervous system because of inadequate removal from portal blood by a diseased liver or as a result of deviation through portal collateral vessels [*6*], may be the toxic agent [*7–10*].

Treatment aimed at reducing the formation of ammonia and other toxic nitrogenous substances in the intestines by withdrawal of protein and the administration of oral broad-spectrum antibiotics [*3*] has had striking results in hepatic coma complicating liver disease of varied etiology [*11*]. To combat the possible role of ammonia in the genesis of coma, glutamic acid was introduced as a therapeutic agent [*12*], but with conflicting reports of its effectiveness [*3,13–16*]. Evidence of deranged intermediary metabolism in hepatic coma [*17,18*] has prompted a trial of lipoic acid [*19*] which facilitates the oxidative decarboxylation of α keto-acids. Cortisone and hydrocortisone have been exhibited in hepatic coma in the hope of improving liver function but experience with these drugs, except in some cases of viral hepatitis, has been disappointing [*20–22*]. Assessment of any therapy is particularly difficult in small, uncontrolled groups of patients owing to the varied prognosis associated with the different factors which may contribute to coma in any individual case, and this may explain the lack of accord concerning the properties of various agents. Moreover, the reported success of protein restriction with antibiotic therapy not only demands more extensive application of this treatment but also raises the possibility that conflicting results with other forms of therapy might be related to associated variations in dietary protein, in supportive measures during their administration, or in the case material studied.

In this paper an attempt has been made to resolve these difficulties by studying two large groups of patients in hepatic coma. One group was treated by protein deprivation and orally administered broad-spectrum antibiotics, the

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TABLE 1

DETAILS OF PATIENTS AND TREATMENT

Patient, Age, Sex	Comments	Duration of Coma (days)	Stage at Which Treated	Serum Bilirubin (mg./100 ml.)	Ascites	Dose and Duration of Specific Therapy	Response to Treatment and Result
Group A—Protein Withdrawal and Antibiotics *No Additional Therapy*							
G. D.† 46, F	Urinary tract infection	8	Coma	13.0	0	.....	Improved, recovered
L. H.‡ 58, M	.....	6	Coma	2.0	+	.....	Improved, died
E. C.† 64, F	Septicemia	10	Coma	3.0	0	.....	Improved, recovered
M. M.† 60, F	.....	7	Coma	2.0	0	.....	Improved, recovered
V. M.† 30, F	.....	19	Impending coma	31.0	+	.....	Improved, died
W. G.† 56, M	.....	5	Impending coma	26.0	+	.....	None, died
B. R.† 29, F	.....	16	Impending coma	6.0	0	.....	None, died
M. S.† 65, F	Massive gastrointestinal hemorrhage, uncontrolled	9	Impending coma	18.4	+	.....	Improved, died
L. G.† 44, F	Septicemia	9	Impending coma	1.7	+	.....	Improved, recovered
J. C.† 41, M	Gastrointestinal hemorrhage, controlled; pulmonary edema after NaCl infusion	7	Impending coma	6.8	+	.....	None, died
O. H.† 34, M	Gastrointestinal hemorrhage, controlled by surgery	7	Impending coma	3.0	+	.....	Improved, recovered
D. G.† 57, M	Gastrointestinal hemorrhage, controlled	5	Impending coma	4.4	0	.....	Improved, recovered
P. T.† 47, M	Gastrointestinal hemorrhage, controlled	5	Coma	2.1	+	.....	Improved, recovered
M. W.† 60, F	Gastrointestinal hemorrhage, uncontrolled, and cardiac failure	8	Impending coma	3.2	0	.....	Improved, died
E. L.§ 63, M	Ischemic heart disease and peripheral vascular failure	18	Impending coma	12.0	0	.....	Improved, died
J. R.† 37, M	.....	22	Coma	33.6	+	.....	Improved, recovered
A. H.‡ 62, F	Septicemia	2	Impending coma	5.8	+	.....	Improved, recovered
F. K.† 54, M	.....	8	Coma	37.8	+	.....	Improved, died
J. D.† 51, M	.....	3	Impending coma	2.6	+	.....	Improved, recovered
H. M.† 48, M	.....	15	Impending coma	33.1	+	.....	Improved, died
Additional Therapy with Protein Withdrawal and Antibiotics							
V. S.‖ 50, M	Terminal gastrointestinal hemorrhage, uncontrolled	9	Impending coma	42.0	+	Protein withdrawal and antibiotics	None
						Cortisone 900 mg. in three days	None
						Lipoic acid 240 mg. in three days	None, died

TABLE I (*Continued*)

DETAILS OF PATIENTS AND TREATMENT

Patient, Age, Sex	Comments	Duration of Coma (days)	Stage at Which Treated	Serum Bilirubin (mg./100 ml.)	Ascites	Dose and Duration of Specific Therapy	Response to Treatment and Result
M. T.† 42, F	Terminal aspiration pneumonia	23	Impending coma	3.0	+	Protein withdrawal and antibiotics	None
						Aspartic acid 12.0 gm. in four hours	None, died
P. S.† 65, M	Gastrointestinal hemorrhage, uncontrolled	4	Impending coma	2.9	+	Protein withdrawal and antibiotics	None
						Aspartic acid 45 gm. in two days	None, died
K. M.† 39, F	Terminal pneumonia	6	Impending coma	6.6	0	Protein withdrawal and antibiotics	None
						Glutamic acid 50 gm. in two days	None, died
K. B.† 53, M	Terminal gastrointestinal hemorrhage, uncontrolled	22	Coma	37.5	+	Protein withdrawal and antibiotics	Improved
						Cortisone 5.8 gm. in twenty days	None
						Lipoic acid 100 mg. in twenty-four hours	None
						Glutamic acid 90 gm. in three days	None, died
J. B.¶ 65, M	Portacaval anastomosis	120	Coma	5.0	0	Protein withdrawal and antibiotics	Improved
				4.6	0	Lipoic acid 100 mg. in twenty-four hours	None
				5.8	0	Glutamic acid 180 gm. in six days	None, died
J. G.** 36, M	.....	18	Impending coma	1.9	+	Protein withdrawal and antibiotics	None
						Glutamic acid 320 gm. in four days	None, died
C. M.† 67, F	.....	17	Impending coma	13.8	+	Protein withdrawal and antibiotics	Improved
						Lipoic acid 400 mg. in four days	None
						Glutamic acid 105 gm. in three days	None, died
C. R.† 37, F	Portacaval anastomosis	5	Coma	4.0	0	Protein withdrawal and antibiotics	None
						Lipoic acid 150 mg. in twenty-four hours	None, died
E. E.‡ 68, F	.....	75	Impending coma	7.1	+	Protein withdrawal and antibiotics	Improved
						Lipoic acid 400 gm. in four days	None
						Glutamic acid 500 gm. in five days	None, recovered
E. S.‡ 70, M	.....	2	Impending coma	3.0	0	Protein withdrawal and antibiotics	Improved, recovered
	Septicemia	37	Impending coma	12.5	+	Protein withdrawal and antibiotics	None
						Lipoic acid 700 mg. in seven days	None, died
F. O.† 32, M	Gastrointestinal hemorrhage, controlled	23	Impending coma	5.7	+	Protein withdrawal and antibiotics	None
						Glutamic acid 100 gm. in four days	Improved
						Lipoic acid 200 mg. in two days	None, recovered

TABLE 1 (*Continued*)

DETAILS OF PATIENTS AND TREATMENT

Patient, Age, Sex	Comments	Duration of Coma (days)	Stage at Which Treated	Serum Bilirubin (mg./100 ml.)	Ascites	Dose and Duration of Specific Therapy	Response to Treatment and Result
S. J.†† 63, F	Gastrointestinal hemorrhage, controlled	4	Coma	1.0	0	Protein withdrawal and antibiotics	None
						Glutamic acid 50 mg. in two days	None, died
R. R.† 49, F	Terminal gastrointestinal hemorrhage, uncontrolled	7	Impending coma	24.0	+	Protein withdrawal and antibiotics	Improved
						Cortisone 600 mg. in two days	None, died
Group B—Protein Allowed during Treatment							
No Specific Therapy							
L. D.† 48, M	Urinary tract infection	16	Impending coma	28.0	+	.....	None, died
M. G.† 46, M	.....	5	Impending coma	19.0	+	.....	Improved, died
R. M.† 76, M	.....	7	Impending coma	4.0	+	.....	None, died
L. V.† 65, M	.....	7	Impending coma	19.0	+	.....	None, died
K. M.† 41, F	Septicemia	24	Impending coma	32.0	0	.....	Improved, died
S. N.† 58, M	Congestive cardiac failure and diamox administration	13	Coma	3.8	+	.....	Improved, died
Glutamic Acid							
T. M.† 58, M	.....	15	Impending coma	37.0	+	92 gm. in two days	None, died
A. P.‡‡ 67, F	Surgical operation, terminal gastrointestinal hemorrhage, uncontrolled	7	Coma	24.0	+	355 gm. in four days	Improved, died
J. W.*† 46, F	.....	5	Coma	24.5	0	175 gm. in thirty-five hours	None, died
J. H.*† 49, F	.....	120	Coma	2.0	+	103 gm. in seventeen hours	Improved, died
L. S.*† 37, F	.....	6	Impending coma	46.0	+	69 gm. in three days	None, died
A. M.*† 54, F	.....	4	Impending coma	22.8	+	23 gm, in twenty-four hours	None, died
G. N.*† 49, M	.....	7	Impending coma	19.2	+	46 gm. in two days	None, died
J. K. *† 67, M	Carcinomatosis	16	Impending coma	9.0	+	69 gm. in three days	None, died
E. C.*† 51, F	Paracentesis abdominis	14	Impending coma	1.7	+	69 gm. in three days	None, died
M. L.*† 64, M	.....	33	Coma	10.0	+	69 gm. in three days	None, died
Cortisone or Hydrocortisone							
F. H.† 45, M	.....	15	Impending coma	38.6	0	Cortisone 1.8 gm. in twelve days	None, died
I. M.† 55, F	Terminal gastrointestinal hemorrhage, uncontrolled	10	Impending coma	29.0	+	Cortisone 9.0 gm. in seven days	None, died

TABLE 1 (*Continued*)

DETAILS OF PATIENTS AND TREATMENT

Patient, Age, Sex	Comments	Duration of Coma (days)	Stage at Which Treated	Serum Bilirubin (mg./100 ml.)	Ascites	Dose and Duration of Specific Therapy	Response to Treatment and Result
H. K.† 52, M	.....	19	Coma	4.0	+	Cortisone 500 mg. in twenty-four hours	Improved, died
J. H.*† 49, F	.....	Vide supra	Impending coma	Vide supra	+	Hydrocortisone 0.7 gm. in six days	None, died
V. A.*† 63, M	Urinary tract infection	44	Coma	1.2	+	Cortisone 0.6 gm. in twenty-four hours	Improved, died
A. G.*† 56, F	Gastrointestinal hemorrhage, pneumonia	28	Coma	6.9	0	Cortisone 1.9 gm. in three days	None, died
J. S.*† 44, M	.....	20	Impending coma	24.0	+	Hydrocortisone 0.57 gm. in eight days	None, recovered
D. C.*† 44, M	.....	7	Coma	11.4	0	Hydrocortisone 1.35 gm. in two days	None, died
J. C.*† 35, F	.....	5	Coma	16.4	+	Hydrocortisone 0.9 gm. in two days	None, died
			Aspartic Acid				
L. C.† 50, M	Gastrointestinal hemorrhage, uncontrolled	15	Impending coma	7.0	+	10 gm. in two hours	None, died
			Lipoic Acid				
H. K.† 52, M	.....	Vide supra	Impending coma	Vide supra	..	40 mg. in two days	None, died
I. B.† 58, M	.....	13	Impending coma	11.0	+	80 mg. in three days	None, died
B. J.† 56, M	.....	24	Impending coma	25.6	+	60 mg. in two days	None, died
J. L.† 68, M	.....	5	Coma	11.6	+	120 mg. in three days	None, died
C. R.† 37, F	Portacaval anastomosis	2	Impending coma	1.0	0	80 mg. in two days	Improved, recovered
G. R.† 43, M	.....	8	Impending coma	25.0	0	400 mg. in four days	None, died

* Reported by Webster and Davidson [*15,23*].
† Cirrhosis of the alcoholic subject.
‡ Cirrhosis of unknown etiology.
§ Ischemic hepatic necrosis.
‖ Carbon tetrachloride poisoning.
¶ Cirrhosis and hemochromatosis.
** Cirrhosis and Wilson's disease.
†† Hepatic lymphoma.
‡‡ Biliary cirrhosis.

patients in the second group received protein during therapy. Some patients in both groups received additional treatment with glutamic acid, aspartic acid, lipoic acid, cortisone or hydrocortisone. Aspartic acid was introduced as a therapeutic agent because effective reduction of blood ammonia concentrations was anticipated, and indeed was obtained on three occasions. The group of patients who received protein included fourteen patients treated with glutamic acid, cortisone or hydrocortisone reported by Webster and Davidson [*15,23*] and four patients treated with lipoic acid by Brin (at whose suggestion lipoic acid therapy was instituted) and his colleagues [*24*].

The relationship of treatment to prognosis and certain associated biochemical disorders, with special reference to deranged metabolism of ammonia and α keto-acids, are considered and the therapy of choice in hepatic coma is discussed.

MATERIAL AND METHODS

Patients Studied. Sixty-three patients were studied consecutively on the general wards of the Boston City Hospital or on the ward of the Thorndike Memorial Laboratory. (Table 1.) Patients who died or recovered within forty-eight hours of admission were excluded as they were often either moribund from uncontrolled complications such as gastrointestinal hemorrhage or, on the other hand, had trivial neurologic disorders which disappeared spontaneously. Nine patients, six of whom died, were considered unsuitable for therapeutic assessment on these grounds. For this reason patients were also excluded if (1) the neurologic disorder was induced solely by agents such as ammonium chloride or diamox,® and (2) when fluctuating chronic neuropsychiatric disturbance was associated with stable liver function and an extensive portal collateral circulation [*4,5*]. Two patients (C. R., E. S.) were admitted in hepatic coma on two separate occasions, thus making a total of sixty-five episodes of coma treated.

Fifty-three patients had hepatic cirrhosis associated with chronic alcoholism and four patients had cirrhosis of uncertain etiology. One instance each of ischemic hepatic necrosis, hemochromatosis, Wilson's disease, hepatic lymphoma, biliary cirrhosis and carbon tetrachloride poisoning accounted for the diagnosis in the remaining six patients. Clinical and biochemical findings were supplemented by histologic evidence from liver biopsy or autopsy in forty-two patients.

Groups of Patients in Relation to Protein Administration. The patients were divided into two main groups. (Table 1.) The thirty-four patients in Group A were treated with a regimen involving exclusion of protein and other nitrogenous substances from the diet, together with the administration of oral broad-spectrum antibiotics and enemas. The thirty patients in Group B received protein during treatment. This group was comprised of twenty-one patients who were studied before the introduction of the Group A regimen (including fourteen patients reported elsewhere [*15,23*]), and nine patients treated subsequently under circumstances in which the indications for protein exclusion were unacceptable. One patient (C. R.) is included in both groups.

Factors which influence the onset of hepatic coma include the state of liver function, the extent of the portal collateral circulation, incidents such as gastrointestinal hemorrhage, intercurrent infection or paracentesis, the previous administration of excess dietary protein or certain drugs, together with pre-existent or coincident disease. A strictly controlled investigation of therapy in the condition is therefore difficult to accomplish and it is not suggested that valid conclusions regarding therapy can be drawn simply from an over-all comparison of results in Group A and B. Rather, some indication is given of the prognosis in relation to protein administration and specific therapy in patients with the same background and treated under the same circumstances. Furthermore, although there are differences in the constitution of the groups, valid inferences concerning treatment can be drawn by comparing results in regard to clinical findings common to patients in both groups.

The Regimens of Treatment. On admission to the hospital, any factors associated with the onset of coma, such as gastrointestinal hemorrhage or intercurrent infection, were treated immediately and drugs known to predispose to hepatic coma (such as ammonium salts, methionine, diamox, opiates, barbiturates, paraldehyde) were withdrawn. Important adjuvant measures included supplements of vitamins, including vitamin K, and potassium chloride. As potassium deficiency may occur, particularly in patients who receive large amounts of carbohydrate without adequate protein, frequent biochemical and electrocardiographic control was exercised. The indications for sodium restriction were based on the presence of edema or ascites. Sedation was given only when strongly indicated; small doses of chlorpromazine or phenobarbital appeared to be tolerated best.

In Group A, protein, amino acid hydrolysates and other nitrogenous substances were excluded from the diet. A daily intake of at least 1,500 calories was maintained with carbohydrate. The administration of this diet depended on the condition of the individual patient but it was most conveniently given in the form of dexin®* (a partially hydrolyzed starch) or 10 to 20 per cent glucose in fruit juice by a slow, intermittent intragastric infusion. Glucose was given intravenously if necessary. When reduction of fluid intake is desirable, solutions of up to 40 per cent can be introduced through polyethylene tubing into a large vein [*11*], thus avoiding the danger of thrombosis of smaller vessels by such concentrated solutions. Chlortetracycline or tetracycline was administered orally or by stomach tube in doses of 1 to 2 gm. daily. Fecal material in the lower intestines was removed by an initial enema, and regular bowel movements were subsequently established by the administration of magnesium sulphate or enemas, depending on the patient's condition and dietary intake.

When unequivocal improvement occurred antibiotics were discontinued and, after forty-eight hours, protein was introduced into the diet in the form of lonalac®† (a low-sodium milk product) or whole milk equivalent to 20 gm. of protein. When there was continued progress, 20 gm. increments of protein were added on alternate days until the patient was restored to a normal diet. Relapse was an indication for immediate return to protein exclusion, antibiotics and enemas.

* Provided through the courtesy of Burroughs Wellcome Co., Tuckahoe, N. Y.

† Provided through the courtesy of Mead Johnson and Company, Evansville, Ind.

TABLE II

SUMMARY OF TREATMENT AND CLINICAL RESPONSE

Specific Therapy	Group A (35 episodes in 34 patients)			Group B (30 patients)		
	Patients	Improved	Recovered	Patients	Improved	Recovered
Glutamic acid	8	1	1	10	2	..
Aspartic acid	2	..	..	1	..	..
Cortisone or hydrocortisone	3	..	..	9	2	1
Lipoic acid	8	..	2	6	1	1

The management of patients in Group B was similar, except that protein was given and broad-spectrum antibiotics and enemas were not specifically included in the treatment. These patients received protein daily in amounts of 60 gm. or less orally or by intragastric tube as lonalac or as part of the ward diet.

Additional Therapy with Specific Agents. Fourteen patients in Group A and twenty-four patients in Group B received therapy in the form of glutamic acid, aspartic acid, lipoic acid, cortisone or hydrocortisone. (Tables I and II.) The criterion for this supplementary therapy in Group A was the patients' failure to improve after forty-eight to seventy-two hours of protein deprivation and antibiotic therapy. L-Glutamic acid*† was given orally or intravenously, as sodium or sodium and potassium glutamate, in amounts from 23 to 400 gm. daily. D,L-Aspartic acid* (10 to 40 gm. daily) was given intravenously as sodium and potassium aspartate. Lipoic acid in the form of sodium-α-lipoate*‡ was administered intravenously or intramuscularly in doses of 20 to 100 mg. daily. On three occasions an intravenous solution containing lipoic acid, 100 mg.; pantethine,§ 20 mg.; magnesium sulphate, 1 gm.; biotin,* 5 mg. and potassium chloride, 3 gm. in 1 L. of 5 per cent dextrose, was given daily. Cortisone* or hydrocortisone * was given intramuscularly in doses of 100 to 700 mg. daily.

Clinical Assessment. Accurate assessment of any therapeutic agent in hepatic coma is impeded by fluctuations in the clinical condition and the frequent disparity between the mental disorder and objective neurologic signs. Consequently, no more than two well defined stages in the syndrome have been recognized in this investigation. The term, "impending coma" is restricted to patients in whom gross mental disorder was associated with objective neurologic disturbance, of which a "flapping tremor" [*1*] was the most common, and "coma" refers to patients who responded only to painful stimuli or not at all. Except when specified, the term "hepatic coma" has otherwise been used to include impending coma.

Patients are classified as "improved" during the course of treatment only if they recovered consciousness after coma, or had no residual neuropsychiatric disorder after an episode of impending coma. "Recovery" indicates that the patient had improved sufficiently to be able to leave the hospital.

Biochemical Methods. Tests of liver function and serum electrolyte determinations were performed in every patient, using standard methods reported earlier [*15*]. Blood ammonia concentrations were measured by a modification [*5*] of Conway's technic [*25*] and blood α-ketoglutarate and pyruvate values were estimated by the method of Seligson and Shapiro [*26*].

RESULTS

Predisposing and Precipitating Factors in Relation to Hepatic Coma. The great majority of patients drank alcohol heavily until admission to the hospital and impaired liver function was the most important factor contributing to coma in nearly all the patients. Elevated serum bilirubin concentrations were almost invariable and more than 60 per cent of the patients in each group had ascites. (Table I.) Gastrointestinal hemorrhage was the commonest contributing factor and precipitated or complicated hepatic coma in twelve instances in Group A and in three patients in Group B. Death was determined by factors other than primary liver disease on four occasions. Three patients in Group A (E. L., M. T., J. C.) died from ischemic heart disease, aspiration of gastric contents, and pulmonary edema following intravenous infusion of saline solution, respectively.

The influence of predisposing factors in the

* Provided through the courtesy of Merck & Co., Inc., Rahway, N. J.

† Provided through the courtesy of Gray Pharmaceutical Co., Inc., Newton, Mass.

‡ Provided through the courtesy of Lederle Laboratories Division of American Cyanamid Company, Pearl River, N. Y.

§ Provided through the courtesy of Parke, Davis & Co., Detroit, Mich.

TABLE III
FACTORS IN PROGNOSIS IN RELATION TO TREATMENT

Data	Group A (35 episodes in 34 patients)			Group B (30 patients)		
	Patients	Improved	Recovered	Patients	Improved	Recovered
Jaundice:						
Serum bilirubin (mg./100 ml.)						
40–20	8	6	1	12	1	1
20– 5	12	7	5	11	..	..
5– 0	15	9	7	7	4	1
Ascites	22	15	8	23	4	1
Gastrointestinal hemorrhage:						
Controlled	6	4	4	1	1	..
Uncontrolled or terminal	6	3	..	2	..	..
Stage at which treated:						
Impending coma	24	15	8	19	..	2
Coma	11	8	5	11	4	..
Duration of impending coma or coma (days):						
2 to 7	15	9	7	12	2	1
8 to 14	7	6	3	6	..	..
>14	13	9	3	12	3	1

genesis of hepatic coma is hard to assess. Stigmas of alcoholism, particularly malnutrition and peripheral neuritis, were frequently present and symptoms of alcohol withdrawal occasionally occurred during hepatic coma. Intercurrent infection was common in the alcoholic patients, occurring in six patients in Group A and five patients in Group B. Septicemia was present in five patients, while three had pneumonia and three had severe urinary tract infections. (Table I.) Although age and sex may have determined prognosis in some patients, these items were found to have no statistical influence in aggregate, thus emphasing the importance of those factors which will be detailed.

Liver Function. Assessment of liver function was based on the presence of jaundice and ascites. Progressive deterioration of liver function with increasing icterus in the alcoholic patient [*27*] was a frequent finding. The incidence of severely jaundiced patients was greater in Group B. On the other hand, liver cell failure sometimes occurred with only mild icterus and four patients with cirrhosis in Group A, who were reformed or non-alcoholics (J. G., M. T., E. E., L. H.), exhibited profound emaciation, ascites resistant to treatment and hepatic coma unrelated to any precipitating factor, in the absence of deep jaundice.

With these reservations, prognosis was clearly related both to the depth of jaundice and the presence of ascites in both groups (Table III), in terms of improvement and recovery. Only two patients with serum bilirubin concentrations greater than 20 mg. per cent recovered (J. R., J. S.). Survival was much greater in patients treated by protein deprivation and antibiotics when icterus was moderate (35 per cent recovery) or relatively mild (50 per cent recovery). A much higher rate of improvement (that is, return to consciousness from coma or complete disappearance of impending coma) was also associated with this therapy. The presence of ascites also indicated a poor prognosis, particularly in patients who received protein. Two-thirds of the patients with ascites in Group A improved but only half of these ultimately recovered. However, this recovery rate far exceeded either improvement or survival in patients in Group B.

Gastrointestinal Hemorrhage. In twelve patients in Group A gastrointestinal hemorrhage precipi-

tated or complicated coma. (Table III.) When hemorrhage was controlled (by balloon tamponage with aspiration of gastric contents, by surgery or by spontaneous arrest) four of six patients recovered. The deaths were due to unrelated causes (malignant lymphoma [S. J.] and pulmonary edema after infusion of saline solution [J. C.]). Gastrointestinal hemorrhage could not be arrested in six patients in this group and all died. In three instances bleeding occurred as a terminal event; except for one (M. W.), all these patients were deeply jaundiced or had ascites, and failure of therapy was presumed to be related to liver disease. Gastrointestinal hemorrhage occurred in three patients in Group B, all of whom died under circumstances comparable to those of the patients in Group A.

Stage at Which Treated. A greater proportion of patients in Group A recovered (nearly 50 per cent) or improved when first treated in coma (33 per cent recovery) than when therapy was instituted during impending coma. (Table III.) The only two patients to recover in Group B had impending coma, although four comatose patients showed transient improvement. From these results there is no evidence that loss of consciousness itself was an adverse prognostic factor in hepatic coma in our patients.

Duration of Neuropsychiatric Disorder. With protein restriction, there was a fair relationship between the duration of neurologic complications and ultimate prognosis. (Table III.) The best results in respect to survival were achieved during the earlier phase of coma in Group A, although a higher proportion of patients with symptomatology of longer duration showed improvement. This reflects the various factors contributing to hepatic coma at different stages of disease. Those who died or recovered during the first week were, in large part, patients with only moderately impaired liver function and mild, transient neurologic disorder (C. R., Group B; J. D., Group A) or with precipitating factors such as gastrointestinal hemorrhage (O. H., D. G., P. T.) which could be readily controlled. However, some patients who deteriorated rapidly (V. M., P. S., S. J., L. M., W. G.) without response to treatment are also included in this group. Patients who survived more than two weeks, on the other hand, include a large number whose initial response to therapy was encouraging but in whom slowly progressive liver failure led to a fatal termination (V. M., H. M., K. B., J. B., E. S.). The mean duration of coma in both groups was similar but a much higher proportion of patients in Group A showed improvement or recovery at each stage, particularly in the earlier phases. (Table III.)

Protein Withdrawal in Hepatic Failure. Deterioration of liver function was the commonest cause of hepatic coma in our patients; malnutrition frequently was an additional factor. Despite these considerations, six patients with serum bilirubin concentrations ranging from 5 to 32 mg. per cent recovered after as long as twenty-two days of protein deprivation and seven others showed improvement on this regimen. These results are in contrast to those in similar patients in Group B who received protein in variable amounts. Three patients (M. G., K. M., S. N.) in Group B were treated initially by protein withdrawal and all showed improvement; subsequently a small daily protein intake of 20 gm. was allowed. Three other patients (L. D., R. M., L. V.) received 20 gm. of protein daily throughout their illness. All these patients exhibited progressive deterioration in liver function while receiving protein and died in hepatic coma.

The Effect of Enemas. The importance of evacuating bowel contents and assuring regular bowel movements subsequently was difficult to assess but is supported by two patients whose recovery from coma appeared to be directly related to bowel function:

Patient J. D. This patient (Table I), was maintained on a 60 gm. protein diet with sodium restriction. Impending coma developed while he was in the hospital. There was no apparent precipitating factor but it was noted that he had had no bowel movement in the previous five days. He improved rapidly following protein withdrawal, chlortetracycline administration and an enema. Subsequently the 60 gm. protein diet was continued but, following three days of constipation confusion and objective neurologic signs again occurred. He was grossly disoriented, exhibiting perseveration of speech and movement, grimacing, catatonia, exaggerated tendon reflexes and a flapping tremor. He was maintained on a constant protein intake despite these findings and treatment by enema alone was followed by rapid recovery.

Patient J. B. This patient (Table I) showed constant mild confusion and tremor over a period of weeks while receiving a 30 gm. protein diet. Rare episodes of stupor responded to the standard treatment. On one occasion stupor followed a three-day period of constipation. A satisfactory enema was fol-

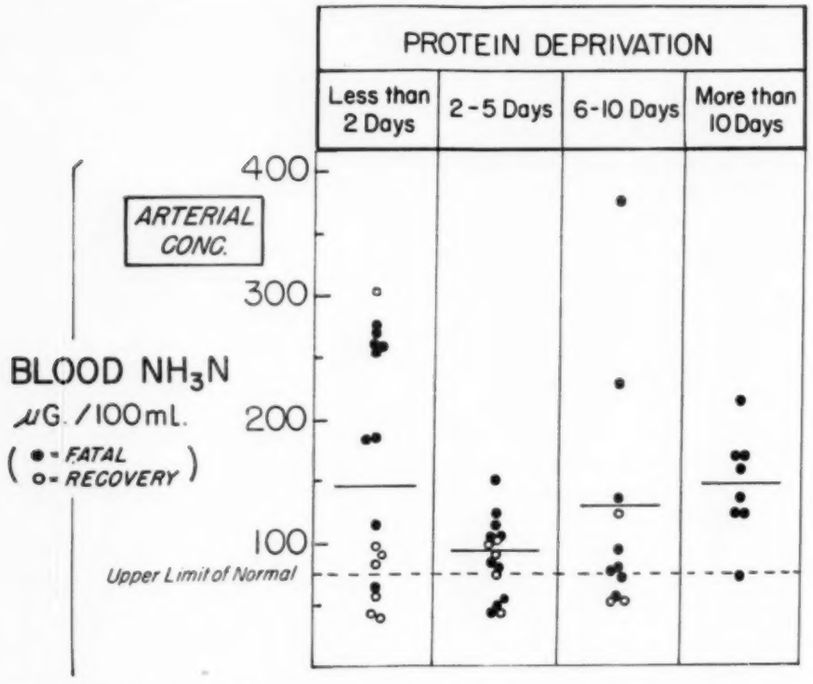

FIG. 1. Arterial ammonia concentrations in relation to treatment by protein withdrawal and oral broad-spectrum antibiotics.

lowed by the patient's recovery within twelve hours, despite continuation of the previous protein intake.

Arterial Blood Ammonia Concentration during Therapy. A relationship between dietary protein and other nitrogenous substances in the intestines and arterial blood ammonia levels during hepatic coma was established in Group A. It was also shown that the elevation of blood α-ketoglutarate and pyruvate concentrations in hepatic coma was related to deranged ammonia metabolism [*28*]. During periods of protein withdrawal and antibiotic therapy there was a decline in arterial blood ammonia concentrations (Fig. 1), which was at its greatest during the fifth to tenth day. Patients who recovered showed an earlier and more profound fall in arterial blood ammonia concentrations, whereas a late elevation, possibly related to release of ammonia from certain tissues or loss of sensitivity of intestinal flora to antibiotics, occurred in fatal cases.

Blood Electrolyte Disorders in Hepatic Coma. The cause and effect relationship of abnormal blood electrolyte concentrations in terminal liver disease is uncertain. The most common pattern observed in our patients was hyponatremia and nitrogen retention, often accompanied by low blood chloride and bicarbonate concentrations. Hypokalemia was inconstant, but serum potassium concentrations below 3.7 mEq./L. were present in six patients in Group A. The changes were most severe in the presence of hepatic failure with ascites, and the patients affected were oliguric with negligible urinary sodium excretion. These patients were on low sodium regimens but in no instance could the biochemical abnormalities be related to paracentesis abdominis.

When present in a severe degree, these changes were associated with a poor prognosis. Five patients were treated with hypertonic saline solution, 200 ml. of a 5 per cent solution intravenously. (Table IV.) On two occasions (L. H., F. K.) transient clinical improvement followed the infusion but it was without effect in the others and patient J. C. died from pulmonary edema subsequent to the procedure. No sustained improvement in clinical condition or urine output was noted in any patient and all eventually died. Elevation of the serum sodium concentration occurred in two patients (C. M., F. K.) but nitrogen retention was more severe following the infusion in both cases.

Specific Therapy. Certain patients in both groups were treated with glutamic acid, aspartic

TABLE IV

SERUM ELECTROLYTE AND NON-PROTEIN NITROGEN CONCENTRATIONS IN PATIENTS WHO RECEIVED 5 PER CENT SODIUM CHLORIDE INTRAVENOUSLY

Patient	Time of Study	Serum Sodium (mEq./L.)	Serum Potassium (mEq./L.)	Serum Chloride (mEq./L.)	Serum Bicarbonate (mEq./L.)	Serum Non-protein Nitrogen (mg./100 cc.)	Comments
L. H.	Before infusion After infusion	110 110	5.6 6.2	84 96	22.0 21.0	40 50	Transient improvement from coma to impending coma
F. H.	Before infusion After infusion	122 125	6.0 ...	.. ..	....	.. ..	No clinical effect
C. M.	Before infusion After infusion	121 129	5.2 6.7	96 88	22.8 24.0	29 81	No clinical effect
F. K.	Before infusion After infusion	128 133	3.5 4.0	82 93	19.6 17.8	50 84	Transient improvement from coma to impending coma
J. C.	Before infusion	108	3.6	79	....	26	Pulmonary edema developed after infusion and patient died

acid, lipoic acid, cortisone or hydrocortisone. (Table II.) In Group A, these drugs were given as adjuvant measures to patients failing to respond rapidly to protein withdrawal and antibiotics, and their use was consequently restricted to those with a less favorable prognosis. The manner in which this investigation was carried out is illustrated in this brief summary:

Patient K. B. This patient (Fig. 2) was a chronic alcoholic. He had cirrhosis and was admitted to the hospital deeply jaundiced and in hepatic coma. Arterial ammonia and α-keto-acid concentrations were greatly elevated. Following protein withdrawal, antibiotic therapy and an enema he recovered consciousness, although residual neurologic disorder persisted. The administration of cortisone, which was continued throughout the illness, failed to influence either the jaundice or the nervous disorder, and addition of a slow intravenous infusion of 100 mg. lipoic acid over twenty-four hours was without clinical or biochemical effect. Despite continued protein deprivation and chlortetracycline, arterial ammonia and α-keto-acid values, which had earlier fallen towards normal, began to rise and the clinical condition deteriorated. Glutamic acid was administered but the patient progressed to coma and no biochemical improvement was apparent. Death, accompanied by a high arterial ammonia value, occurred following terminal gastrointestinal hemorrhage.

Glutamic Acid. Results in nine patients in Group B who received glutamic acid have been reported earlier [*15*]. All these patients died and seven had severe impairment of liver function. Transient improvement during therapy occurred in only two patients (J. H., A. I.), both of whom received large doses.

Glutamic acid was given to nine other patients in this study, one of whom (T. M.) was receiving protein, and improvement was observed once only, when gastrointestinal bleeding precipitated coma in a mildly jaundiced patient (F. O.). Three patients had severe icterus (K. B., C. M., T. M.), but serum bilirubin concentrations ranged between 1.0 and 7.1 mg./100 ml. in the other patients who failed to respond (J. B., J. G., E. E., S. J., K. M.). Glutamic acid, therefore, failed to improve the prognosis in Group A and was of dubious value in the remainder of the patients.

Aspartic Acid. Three patients received aspartic acid intravenously and all eventually died. Coma was related to gastrointestinal hemorrhage in two patients (P. S., C. L.); the third patient (M. T.) had advanced liver disease but died ultimately from aspiration of stomach contents.

There was evidence that aspartic acid affected

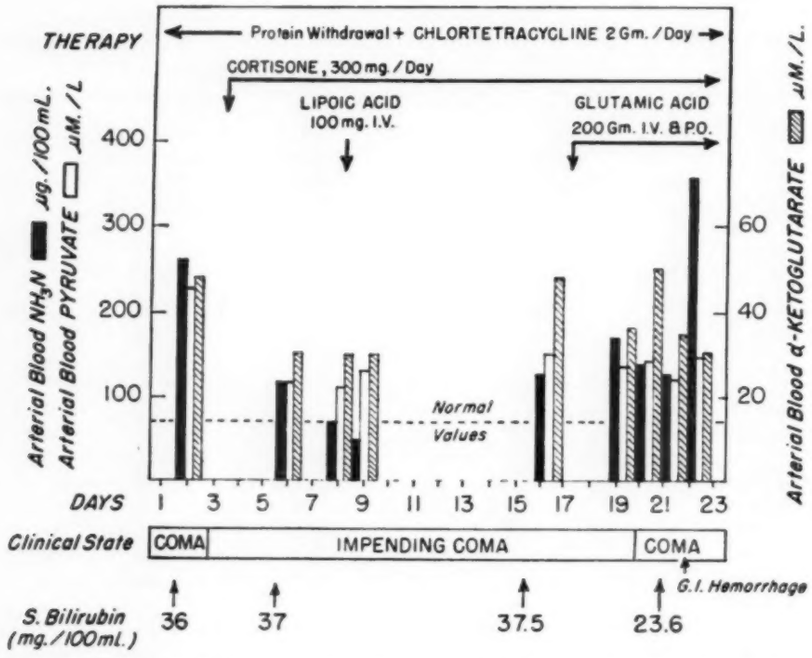

FIG. 2. Patient K. B. Neuropsychiatric state and biochemical findings in relation to treatment during hepatic coma.

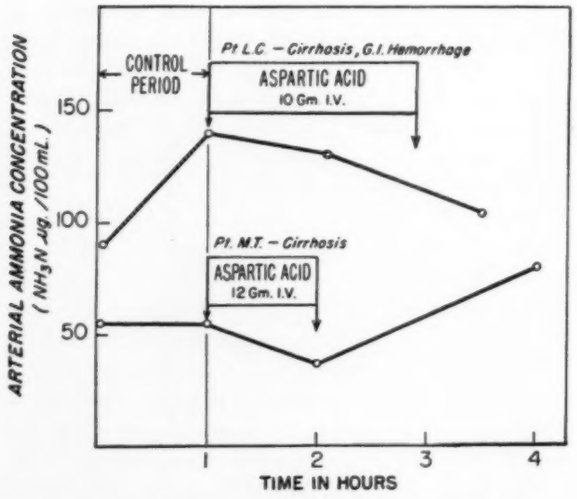

FIG. 3. Arterial ammonia concentrations during intravenous aspartic acid in two patients in hepatic coma.

the arterial ammonia concentration. (Fig. 3.) In patient M. T. arterial values were steady in the control period and fell during administration of the drug. Subsequently there was a rise to above the fasting value. Patient L. C. received the drug three hours after hematemesis and arterial ammonia concentrations were rising during the control period. When the drug was given the elevation of blood ammonia values was halted and the levels later began to fall.

None of the patients improved during this therapy; all had ascites, although none was heavily jaundiced.

Cortisone and Hydrocortisone. Six of the nine patients who received these drugs and protein were studied earlier [*23*]. Transient improvement was observed only in patient V. A. In no instance was liver function improved and the only patient to recover finally (J. S.) was not influenced by this therapy. Subsequent experience with six more patients, equally divided between Groups A and B, confirmed the lack of improvement in liver function or neurologic state in response to cortisone. These patients (F. H., I. M., J. K., K. B., V. S., R. R.) all had severe liver disease and all died; moreover, on four occasions death was due to gastrointestinal hemorrhage which complicated therapy.

Lipoic Acid. Lipoic acid was given to fourteen patients. (Tables I and II.) In nine patients (K. B., C. M., E. E., E. S., V. S., I. B., B. J., J. L., J. R.) severe liver disease was judged the basis of coma and none improved. Four patients had better liver function (J. B., F. O., J. K., C. R.) and only C. R. showed any improvement. This patient was admitted to the hospital twice

and recovered from impending coma while receiving lipoic acid on the first admission. Subsequently, she was admitted in coma and died despite this treatment.

The effects of lipoic acid on arterial ammonia and α keto-acid concentrations were studied in six patients who received concurrent therapy with protein deprivation and antibiotics. (Table v.) The biochemical abnormalities improved towards normal in three patients (J. B., C. M., E. E.) but deterioration occurred in two others (C. R., F. O.).

No influence could be attributed to the administration or withholding of protein in relation to lipoic acid therapy, nor did the dose, which varied between 20 and 100 mg. daily, or the duration of the dose affect results. The combination of pantethine, biotin, magnesium sulphate and potassium chloride with lipoic acid in three patients (K. B., C. R., F. O.) had no added therapeutic action.

Incidental Clinical Observations. The neuropsychiatric syndrome incident to hepatic coma has been extensively documented [*1,3,4,29,30*] but certain diagnostic difficulties in patients in Group A are worth stressing. The preponderance of chronic alcoholic patients studied drew attention to the incidence of alcohol withdrawal disorders during the course of hepatic coma, including two instances of delirium tremens (F. O., W. G.). Identification of this condition was difficult as hallucinations and an abnormally fine tremor may occur in hepatic coma. Similarly, confabulation may complicate the latter condition, and coexistent Korsakoff's psychosis was temporarily overlooked in one patient (K. B.). Muscular rigidity, hyper-reflexia and clonus in the lower limbs are frequent findings in hepatic coma [*31*] but were rare in this series, presumably owing to the presence of peripheral neuritis. One patient (C. R.) presented with Jacksonian convulsions and in two patients (M. M., E. C.) the combination of generalized muscular rigidity, increased reflexes, ankle clonus and extensor plantar responses resulted in an initial diagnosis of cerebral vascular accident. Other uncommon presenting signs included bizarre choreoathetoid movements with grimacing (E. E.), a manic-depressive state without objective neurologic disorder in the early stages (M. T.), and catatonia (J. D. and G. D.). In two patients impending coma and coma alternated for four months (J. B., J. H.). This followed construction of a portacaval anastomosis with the coincident development of jaundice and edema in one patient (J. B.), and slowly progressive deterioration in liver function led to the death of both patients. In one patient hepatic coma developed due to severe hepatic necrosis secondary to prolonged peripheral vascular failure complicating ischemic heart disease.

TABLE V

ARTERIAL AMMONIA, PYRUVATE AND α-KETOGLUTARATE CONCENTRATIONS BEFORE AND AFTER ADMINISTRATION OF SODIUM LIPOATE

Patient	Time of Study	Ammonia (75 μg./100 ml.*)	Pyruvate (160 μM./L.*)	α-Ketoglutarate (15 μM./L.*)
J. B.	Before administration	82	243	25.1
	After administration	43	215	25.5
C. M.	Before administion	175	202	50.2
	After administration	135	148	38.4
E. E.	Before administration	43	135	37.7
	After administration	53	81	30.2
K. B.†	Before administration	71	111	34.5
	After administration	44	131	34.6
C. R.†	Before administration	122	161	37.8
	After administration	185	182	39.1
F. O.†	Before administration	53	61	8.8
	After administration	123	104	13.4

* Upper limit of normal.

† Sodium-α-lipoate with pantethine, biotin, magnesium sulphate and potassium chloride.

Fetor hepaticus was almost invariably noted. This disappeared on protein withdrawal [*32*] but elimination of fetor did not necessarily improve the prognosis.

COMMENTS

Assessment of therapy and prognosis in hepatic coma demands consideration of the various factors which may contribute to its genesis. The majority of patients in the series reported here had severe liver disease and a relationship between liver function, as expressed by the criteria of jaundice and ascites, and prognosis [*11,13*] was soon apparent. Prognosis was relatively poor in the presence of ascites or with icterus

exceeding serum bilirubin concentrations of 5 mg. per cent. Sherlock et al. [*11*] came to the same conclusion, except that serum bilirubin concentrations greater than 3 mg. per cent carried an adverse prognosis in their non-alcoholic patients with cirrhosis. The additional influence of malnutrition and other disorders incident to chronic alcoholism in our patients could not be determined. The etiologic and prognostic significance of the intercurrent infections to which they were prone was also problematic.

Coma associated with gastrointestinal hemorrhage or other complications amenable to treatment responded to therapy relatively well, provided that the cause was readily controlled. Blood in the intestines, however, may cause neurologic complications in subjects with liver disease [*33*] regardless of the more general physiologic consequences of hemorrhage, and immediate arrest of bleeding was considered mandatory. This was best achieved in patients with bleeding esophageal varices by cardioesophageal balloon tamponage [*34*], with aspiration of blood from the stomach. The immediate outlook is also favorable in patients with stable liver function in whom coma is associated with either the injudicious exhibition of drugs such as ammonium salts or with chronic intolerance of dietary protein [*3,4,11,13*]. Such patients were excluded from this study, together with those in whom only mild personality changes were present, as their rapid response to therapy would tend to bias results. The relatively favorable prognosis under these various circumstances is accepted and has encouraged separation of such cases as examples of "exogenous" coma, in contradistinction to spontaneous coma due to liver failure [*14,15*]. However desirable from the clinical standpoint, such a distinction is difficult to maintain as the neuropsychiatric, electroencephalographic and biochemical findings reported in hepatic coma are common to both groups and, as was evident from our patients, both factors are frequently operative in the same subject.

The prognosis was clearly related to the duration of coma, and chances for survival became progressively less when neurologic signs persisted after more than a week of therapy. Loss of consciousness is regarded as ominous [*11,35*], but whether treatment was instituted in coma or impending coma had little influence on recovery in this series.

Patients treated by protein withdrawal and broad-spectrum antibiotics fared much better than those who received other treatment in association with protein feeding in this hospital. Moreover, results compared favorably with those achieved recently elsewhere in large series of patients. Of thirty-four patients in acute coma, 37 per cent recovered and 60 per cent improved during treatment. McDermott and others [*13*], using glutamic acid, reported 20 per cent survival and 55 per cent improvement. The 7 per cent survival in our patients who received protein is probably representative of the prognosis in a series containing a high proportion of alcoholic patients with severe liver disease and associated disorders, and agrees with the experience of Schwartz and others [*16*]. The prospect of recovery after loss of consciousness is assessed at 10 per cent by Foulk et al. [*35*] but 45 per cent of comatose patients treated by protein withdrawal and antibiotics recovered.

The rationale of protein deprivation and broad-spectrum antibiotic therapy rests on inhibition of the formation of toxic nitrogenous substances in the gastrointestinal tract. Identity of the substance which gains access to the nervous system due to impaired hepatic metabolism is uncertain, and the relative importance of protein withdrawal, antibiotics and enemas in the success of the regimen is impossible to evaluate at present. Diets containing 120 gm. protein may precipitate coma in patients with cirrhosis [*2*] and occasionally patients are sensitive to a daily intake of as little as 20 gm. [*4*]. When there is deterioration of liver function, very small amounts are therefore likely to be dangerous and regimens which happened to contain no protein have been recommended previously in hepatic coma [*36*]. Similarly, the administration of chlortetracycline in the absence of protein restriction was considered to improve prognosis in hepatic coma [*37*]; this drug was later shown to protect sensitive patients from hepatic coma provoked by methionine [*38*]. Fisher and Faloon [*39*] achieved the same effect during protein administration with larger daily doses of neomycin, but the antibiotic of choice and optimal dosage have yet to be determined. There is no evidence that chlortetracycline has a beneficial action on the liver in man, although the nature of its presumed action on the metabolism of the intestinal flora in relation to hepatic coma has defied extensive investigation [*38*]. It is logical to include enemas in any regimen directed at reducing absorption of metabolites from the intes-

tines, especially as absorption of toxic substances occurs from the lower bowel [*40*]. The recovery of two patients who received enemas alone supports inclusion of this measure.

Abnormalities of ammonia metabolism in hepatic coma [*6,9,28*] have raised the possibility of ammonia intoxication as a causal factor, and the consequent use of glutamic acid and aspartic acid in this study. Theoretically, amidation of these compounds should remove ammonia with formation of glutamine or asparagine, and asparagine itself has been shown to reduce blood ammonia concentrations [*41*]. The conflicting reports on the efficacy of glutamic acid have been attributed to its therapeutic inadequacy in the presence of severe liver disease, in contrast to its success in other patients, particularly those with gastrointestinal bleeding or chronic protein intolerance [*13*]. The prognosis of these latter conditions is relatively good with protein withdrawal, however, and it was not possible to demonstrate additional benefit from glutamic acid under any circumstances, except perhaps for fleeting improvement following very large doses [*15*]. Aspartic acid was also ineffective in our limited experience. Glutamic acid reduces peripheral vein ammonia values under some circumstances [*11,13,15*], but observations are preferably made on arterial blood [*9*] and should take into account the effect of ammonia derived from food or blood in the gastrointestinal tract [*28*]. Aspartic acid depressed arterial ammonia concentrations, but the infusion was followed by a rise in one patient. A similar elevation may follow the infusion of glutamic acid in patients with severe liver disease [*42*]. Therefore, it seems likely that both drugs may sometimes defeat their object, presumably due to their subsequent deamination. On the other hand, protein withdrawal and antibiotics consistently lowered arterial ammonia concentrations, although after several days there was a rise in fatal cases. Perhaps this was due to the release of ammonia by certain tissues or to the development of an intestinal flora resistant to the antibiotic. Nevertheless, the less predictable biochemical and clinical effects of glutamic and aspartic acids suggests that their use should be reserved for exceptional circumstances such as progressive coma due to uncontrolled gastrointestinal hemorrhage.

Lipoic acid was given to facilitate oxidation of the α keto-acids, which accumulate in hepatic coma [*17,18*] and this accumulation appears to be related to impaired ammonia metabolism [*28*]. However, lipoic acid failed to exert any clinical or consistant biochemical effect. The metabolism of carbohydrate is disordered at the stage of pyruvate oxidation in hepatic coma [*43*] and our failure to reproduce the depression of keto-acid levels reported by Thompson and others [*44*] may have been related to the relatively large glucose intake in our patients.

Our results with these various drugs under controlled conditions were, as has been indicated, disappointing but it should be pointed out that the nature of the trial decreed that no patient received these specific agents under ideal circumstances. The rare favorable response to these drugs might well have been due simply to natural fluctuations in the course of the illness or to a delayed response to protein withdrawal. It is therefore reasonable to suggest that the therapeutic qualities attributed to them in previous investigations might often have been due to their exhibition in patients whose prognosis was comparatively good under any circumstances [*16*], or to the coincident exclusion of protein from treatment in the comatose patient.

Protein exclusion and oral broad-spectrum antibiotic therapy thus emerges as the therapy of choice in our experience, a result in accord with that of Sherlock et al. [*11*], whose recovery rate of 50 per cent in acute coma included patients with liver disease of varied etiology. The less impressive survival in our patients may be due to the preponderance of alcoholic patients with severe liver disease. In both series failure of treatment was related closely to the severity of the liver disease, and therapy directed towards improvement of liver function therefore becomes an important consideration. In some patients hepatic disease had doubtless progressed beyond rehabilitation but in others, particularly in those with "acute hepatic insufficiency of the alcoholic" [*27*] or "florid cirrhosis," [*45*] recovery might have been possible if they could have been sustained through the period of acute decompensation.

The traditional relationship between protein malnutrition and certain types of liver disease might seem to contraindicate therapy based on protein withdrawal and chlortetracycline, especially as this drug results in a negative nitrogen balance [*46*]. A daily protein intake of at least 50 to 75 gm. daily in hepatic coma is recommended [*47*], although nitrogen balance can usually be maintained on considerably lower

protein diets in liver disease [*11,48*]. The administration of 20 gm. of protein daily failed to improve survival rates, and long term protein deprivation appeared to do more good than harm in patients with hepatic failure even though many of those who improved initially ultimately succumbed.

Attempts to improve liver function with cortisone or hydrocortisone were unsuccessful, and the high incidence of gastrointestinal hemorrhage suggested strongly that cortisone, in fact, added to the hazards of hepatic coma. Earlier work with methionine, which may be dangerous in hepatic coma [*38*], and choline [*49*] has failed to establish that the dramatic response obtained in experimental animals with nutritional cirrhosis occurs in human subjects with liver disease. It may be, however, that the improved nitrogen tolerance brought about by antibiotics [*38,39*] will permit a greater protein intake in hepatic failure without prejudicing the nervous system. Alternatively, the use of intravenous amino acids might be feasible, although the production of rising blood ammonia concentrations and impending hepatic coma in response to this measure [*38,50*] would seem to contraindicate such treatment.

Hepatic failure necessarily implies a widespread metabolic disturbance and, although the syndrome of hepatic coma is prominent under such circumstances, additional disorders may contribute to death. Deranged fluid and electrolyte control was often associated with severe impairment of liver function but attempts to correct this by infusion of hypertonic saline solution or administration of potassium supplements were of dubious benefit, indicating that such treatment should be undertaken with caution. It is doubtful, however, that the poor prognosis in this group can be improved until additional factors of importance incident to liver failure are identified and appropriate treatment is delineated.

In conclusion, a regimen of protein withdrawal, oral broad-spectrum antibiotics, enemas and vigorous treatment of any precipitating factor is the recommended therapy for hepatic coma. This regimen is simple to apply and provides a stable basis for trial of other measures for purposes of determining their comparative effectiveness, reducing access to the body of ammonia and other toxic nitrogenous substances, one or more of which are believed to be the causal agents in hepatic coma, whereas more specific therapies are aimed at the correction of a metabolic disorder which is as yet undefined. The improved prognosis of this regimen however remains less than satisfactory. Particular attention should be directed towards hepatic failure as the object of further therapeutic advances in hepatic coma.

SUMMARY

The response to treatment in sixty-five episodes of hepatic coma was studied in sixty-three patients. Thirty-four patients were treated with a regimen of protein withdrawal, oral broad-spectrum antibiotics and enemas, which had the object of reducing the formation and absorption of toxic nitrogenous substances of intestinal origin. Twenty-one patients improved during treatment and thirteen recovered. Of thirty patients who received varying amounts of protein during hepatic coma, five showed improvement and two survived, but the two groups were not entirely comparable. Additional therapy with glutamic acid, aspartic acid, cortisone, hydrocortisone or lipoic acid was given on forty-seven occasions. No additional benefit could be attributed to the exhibition of these specific agents, and it was concluded that the therapy of choice was protein withdrawal and oral administration of broad-spectrum antibiotics.

The majority of those treated were alcoholic patients with severe liver disease, and hepatic function was the most important factor in prognosis. Protein withdrawal and antibiotics reduced arterial blood ammonia concentrations. Like glutamic acid, aspartic acid had a transient effect on blood ammonia values in two patients. Lipoic acid had no constant effect on arterial blood ammonia, pyruvate or α-ketoglutarate concentrations.

Acknowledgment: The authors gratefully acknowledge the technical assistance of Miss A. Ballou, Miss L. DeCarli and Miss E. Hirshberg and the dietetic services of Miss E. Antonaros and Miss M. Bradley. We are also grateful for the cooperation of the staff of the Boston University, Harvard and Tufts Medical Services.

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The "Dieting Depression"*

Incidence and Clinical Characteristics of Untoward Responses to Weight Reduction Regimens

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In recent years the ill effects ascribed to excessive body weight have received wide attention, as have the benefits to be achieved by weight reduction. As a result many physicians and their patients who had formerly looked upon weight reduction as a cosmetic conceit have now come to consider it a therapeutic imperative. The over-all results may well be desirable. But the findings of this report indicate that for a large number of overweight persons the current widespread prescription of reducing diets has had unfortunate consequences; for a smaller number it has been disastrous.

Unexpected as they may be, these considerations have been foreshadowed by earlier reports. Accounts of famines are replete with instances of the suffering and behavior disorders which occur in starving persons [*1*]. More recently Keys and his associates have defined with some precision the character of the "semistarvation neurosis" which occurred during drastic weight reduction of a group of healthy young men [*2*]. There persists a belief, however, that semistarvation undertaken for therapeutic purposes does not involve such hazards, and the literature on obesity contains surprisingly few references to the untoward effects of weight reduction regimens on obese persons.

Physicians treating obese persons, on the other hand, have long noted widely varying responses to weight loss, from the patient who has never felt better in his life to the one who becomes so weak that he can hardly keep going. Furthermore, anorexia nervosa is frequently reported as beginning during a reducing regimen [*3*]. Hertz and Means were among the first to document the problem in their 1936 report on the precipitation of thyrotoxicosis by weight loss arising either from voluntary restriction of food or from debilitating illness [*4*]. In 1947 Federn noted that "some schizophrenic processes are initiated by intentional reducing or gaining of weight," and surmised that "in his proprioceptive sensation of the oncoming psychosis the patient is inclined to overdo an otherwise rational dieting" [*5*]. In 1951 Hamburger reported that of a group of eighteen obese patients seen by him for psychiatric treatment or consultation six patients "developed emotional upsets when they lost weight" [*6*]. In the following year Bruch contributed detailed descriptions of psychotic reactions apparently precipitated by attempts at weight reduction [*7*].

A previous report on the "night-eating syndrome" noted that nine of twenty-five obese patients in a special study clinic had experienced severe emotional disturbances during past or current attempts at weight reduction [*8*]. The present report describes these "dieting depressions" in greater detail.

INCIDENCE OF UNTOWARD REACTIONS TO ATTEMPTS AT WEIGHT REDUCTION IN A NUTRITION CLINIC

There are no published reports of the incidence of untoward reactions to weight reduction programs, and any attempt to determine such incidence meets an obstacle encountered in all clinical investigation of obese persons—their tendency to discontinue treatment. Carefully reported series reveal that from 20 to 80 per cent of patients beginning weight reduction regimens

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abandon them before their completion, and thus are not available for further study. These are precisely the patients who are of the greatest interest from the point of view of untoward responses.

An attempt was made to determine a true incidence of untoward responses to weight reduction programs by interviewing one hundred consecutive obese persons requesting reducing diets at the Nutrition Clinic of the New York Hospital. During the routine interview the dietitian took a history of any previous attempts at dieting.* No diagnostic formulation was made but the presence and character of the symptoms were recorded.

TABLE 1
INCIDENCE OF UNTOWARD REACTIONS TO WEIGHT REDUCTION REGIMENS (PER CENT)

Symptoms	100 Obese Patients in a Nutrition Clinic	32 Healthy Volunteers of Normal Weight during Semi-starvation
Weakness	21	81
"Nervousness"	21	..
Anxiety	..	16
Restlessness	..	41
Irritability	8	44
Fatigue	5	88
Nausea	4	3
Difficulty in concentration	..	66
"More often downhearted"	..	62
Apathy	..	34

Table 1 compares symptoms occurring in the group of 100 obese patients during therapeutic weight reduction regimens with those which were reported by subjects of the Minnesota experiment [2]. The prolonged semistarvation of the latter subjects imposed a far greater stress than the desultory dietary attempts of the obese patients, and a higher incidence of symptoms resulted. It is nevertheless of interest to note the similarity and relatively high incidence of symptoms provoked by what is generally considered a benign form of therapy.

Comparison of the results with those reported by Keys and Brozek is instructive [2]. The circumstances of the two studies vary greatly. The Minnesota project involved thirty-two healthy young men of normal weight who lost 25 per cent of their body weight over a six-month period. The physical stress to which these persons were subjected was thus very severe; in all of them, for example, nutritional edema developed during the course of the program. Many of the obese women, on the other hand, discontinued their diets before they had lost even 10 pounds. Furthermore, the Minnesota subjects reported their symptoms on a check sheet during the period of dieting; in contrast, the nutrition clinic study was retrospective and recorded only symptoms which were volunteered. Each of these differences would be expected to increase the incidence of untoward symptoms in the Minnesota subjects, and a higher incidence was in fact observed in this group. What was surprising, however, was the large number of persons in the nutrition clinic who reported similar responses to dieting.

Of the one hundred patients requesting diets, seventy-two had attempted dieting previously, several on more than one occasion. Of these seventy-two patients 54 per cent reported the presence of symptoms during at least one reducing regimen, and 55 per cent of all such regimens were characterized by the presence of symptoms. As will be seen in Table 1, a common symptom was "nervousness" which included both anxiety and restlessness, and which was present in 21 per cent of the patients. "Weakness" was reported by 21 per cent, and "irritability" by 8 per cent. Other complaints were less frequent, "fatigue" (5 per cent) and "nausea" (4 per cent). The figures for each of these complaints are noted in Table 1, together with the corresponding values for the Minnesota subjects. At the bottom of the table is included the incidence of common symptoms reported by the Minnesota subjects but not by the patients from the nutrition clinic.

ROLE OF DIETING IN A SMALLER GROUP

Method. The high incidence of symptoms reported by the nutrition clinic patients renders more understandable the poor results of weight reduction programs, and makes it important to learn more about the nature of these untoward responses. For this purpose a more detailed study of twenty-five obese persons was undertaken. These patients were seen in a special study clinic of the New York Hospital where they had been sent from other departments because of the severity of their obesity or difficulty in its management. The group may thus be presumed to in-

* A more complete report of this study, undertaken in collaboration with Mrs. Mavis Hume, is now in preparation.

clude a high proportion of emotionally disturbed persons but whether or not this proportion is higher than in any group of comparably severe obese persons is conjectural. It should be noted that only two of the patients were men.

In the earlier report on the night-eating syndrome further characteristics of this same group of patients were outlined and will not be detailed here [*8*]. Vital statistics of the patients, and the setting and clinical characteristics of their illnesses are summarized in Table II. For convenience in referring to the previous report the numbers assigned to patients in this table are those used in the earlier paper. Three discrepancies between the tables will be noted. One of the illnesses of patient No. 1, D. M., occurred after publication of the previous report, and only at this time was it learned that an earlier illness had occurred during a reducing regimen. The complications of the weight reduction program reported by patient No. 6, M. L., were not of sufficient severity to include them in the present report.

Setting of the Illnesses. Reference to Table II reveals striking evidence of the difficulty experienced by these patients in their efforts to lose weight. Attempts at dieting were associated with severe emotional disorders in nine of the twenty-five patients. Four such disorders occurred while the patients were being treated in the special study clinic; eight others occurred at various times as noted in Table II. (Three of the patients experienced two illnesses each.)

The high incidence of symptoms during dieting suggests that weight reduction may be dangerous for some obese persons. Two questions, however, arise. First, is the concordance of dieting and emotional disorder higher than would occur by chance alone? Second, is the dieting itself perhaps no more than an incidental symptom of a pre-existing emotional disorder? Dieting is such a common activity of obese persons that the apparent correlation between it and emotional disturbance could represent no more than the frequent but entirely random coexistence of two unrelated variables. The evidence, however, is against this. In the entire non-dieting experience of the twenty-five patients in this series, there were only five illnesses of comparable severity. In contrast, during the far shorter period of time in which the patients were dieting there were twelve such illnesses. Analysis of these data by means of the chi-square test reveals that the probability of this distribution of illness occurring by chance alone is less than 5 per cent.

There remains the second possibility that for these patients dieting may itself be a symptom of the emotional disorder, so that the presence of other symptoms is only to be expected. Although the dieting clearly was of significance in the emotional equilibrium of these patients it did not appear to be a symptom of emotional disorder in the sense implied by Federn. None of the patients was disorganized at the time she undertook a reducing regimen, nor did this undertaking appear to represent a defense against such disorganization.

An attempt was made to determine whether any characteristic of either the patients or the diets might be associated with the occurrence of illness during a weight reduction regimen. Many of the patients were emotionally disturbed before undertaking the diet, but so were a number who experienced little difficulty during dieting. Furthermore, there was no common premorbid personality type, and untoward responses occurred in patients with a variety of psychiatric diagnoses. The age at onset of illness, too, varied widely, one patient being only seventeen years old, another forty-two. All the patients were women, but this may reflect no more than the selection of the original population of twenty-five obese persons, twenty-three of whom were women.

The character and duration of the weight reduction regimen did not seem to play a role in the precipitation of the illnesses. A wide variety of diets were used by the twenty-five subjects in the special study clinic and none seemed to be associated with a higher incidence of complications. Furthermore, the duration of dieting before the onset of symptoms varied widely, as did the amount of weight lost. One patient became ill within two weeks after starting to diet, while another was essentially asymptomatic for a year. The first of these patients had lost only twelve pounds; the latter had lost 150.

One factor which was common to the persons who fell ill was a tendency to manifest the night-eating syndrome. In the previous report [*8*] it was noted that this pattern of nocturnal hyperphagia, insomnia and morning anorexia was present in twenty of the twenty-five subjects comprising the present series, and in none of thirty-eight non-obese women. The pattern occurred during periods of life stress, and its presence was associated with a high incidence

TABLE II

Identifying Data						Setting of Illness					Symptomatology										
														Period of Depression							
No.	Patient	Age (yr.)	Height	Weight (lb.)	Overweight at Time of Illness (%)	Premorbid Psychiatric Diagnosis	Night Eating Syndrome	Interpersonal Setting	Duration of Diet before Onset of Symptoms (mo.)	Weight Loss before Onset of Symptoms (lb.)	Duration of Illness (mo.)	Period of Elation	Period of Anxiety	Depression of Mood	Crying Spells	Insomnia	Feelings of Futility	Self Reproaches	Work Incapacity	Retardation	Weight Change (lb.)
ILLNESSES ASSOCIATED WITH DIETING IN GROUP OF TWENTY-FIVE OBESE PERSONS																					
1	D. M.	18	5′0″	180	61	Schizophrenic reaction	+	Leaving home to attend college	4	30	12	+	+	+	+	+	+	0	+	0	+75
		24	5′0″	275	137		+	Attempt to break with mother	½	12	6	+	+	+	+	+	+	0	+	0	+15
2	H. G.	42	4′10½″	400	220	Passive aggressive personality	+	Departure of physician on whom she depended	12	150	3	0	+	+	+	+	+	0	+	0	+50
3	L. M.	24	5′2″	260	110	Passive aggressive personality	+	Information inadequate	3	50	6	?	?	+	+	?	+	0	+	?	+35
9	E. M.	34	5′2½″	238	84	Schizoid personality	+	Attempt at independence of husband by (fantasy) love affair with physician	46	45	9	+	+	+	+	+	+	+	+	0	0
10	A. R.	27	5′4″	235	81	Passive dependent personality	+	Information inadequate	4	50	2	0	+	0	0	+	+	0	+	0	+35
12	L. S.	17	5′2½″	160	37	Passive dependent personality	+	Attempt to become glamorous, escape from drab life	0	0	3	0	+	+	+	+	+	0	+	0	+20
		27	5′2½″	220	77		+	Attempt at independence of neighbor	1½	18	5	+	+	+	+	+	+	0	+	0	+15
19	M. C.	49	5′0″	183	39	Compulsive personality	+	Attempt at independence of family by (fantasy) love affair with physician	3	13	12	+	+	+	+	+	+	0	+	+	−25
20	S. G.	25	5′3″	180	45	Obsessive compulsive reaction	+	Physician's threat that she would die unless she lost weight	2	45	2	0	+	+	+	+	+	0	+	0	+15
		31	5′3″	210	64		+	Fear of "losing husband" by her own death unless she lost weight	10	70	10	0	+	+	+	+	+	0	+	0	0

TABLE II (*Continued*)

Identifying Data						Setting of Illness					Symptomatology											
														Period of Depression								
No.	Patient	Age (yr.)	Height	Weight (lb.)	Overweight at Time of Illness (%)	Premorbid Psychiatric Diagnosis	Night Eating Syndrome	Interpersonal Setting	Duration of Diet before Onset of Symptoms (mo.)	Weight Loss before Onset of Symptoms (lb.)	Duration of Illness (mo.)	Period of Elation	Period of Anxiety	Depression of Mood	Crying Spells	Insomnia	Feelings of Futility	Self Reproaches	Work Incapacity	Retardation	Weight Change (lb.)
24	S. S.	27	5′2½″	136	11	Cyclothymic personality	+	Breaking off (homosexual) love affair	7	28	5	0	+	+	+	+	+	0	+	+	0
ILLNESSES NOT ASSOCIATED WITH DIETING IN GROUP OF TWENTY-FIVE OBESE PERSONS																						
2	H. G.	19	4′10½″	120	9	Passive aggressive personality	..	Return home at mother's insistence after attempt at independent living	....	...	12	0	0	+	+	+	+	0	+	0	0
6	M. L.	25	5′5″	255	95	Schizophrenic reaction	..	Broken engagement	....	...	6	0	Anxiety present throughout illness	+	+	+	+	0	+	0	+10
18	L. C.	30	4′9½″	166	43	Schizoid personality	..	Broken engagement	....	...	12	0	Anxiety present throughout illness	+	+	+	+	0	+	0	0
20	S. G.	34	5′3″	176	35	Obsessive compulsive reaction	..	Departure of physician on whom she depended	....	...	6	0	Anxiety present throughout illness	+	+	0	+	+	+	0	+30
24	S. S.	30	5′2½″	145	16	Cyclothymic personality	..	Conflict over breaking off (homosexual) love affair	....	...	12	0	Anxiety present throughout illness	+	+	+	+	0	+	+	0

of complications of weight reduction regimens. Thus of the twenty subjects who manifested the night-eating syndrome only eleven were ever able to lose more than one-third of their excess weight, and in nine of these subjects this weight loss was accompanied by the untoward reactions which will be described. Four of the five subjects who showed no tendency toward the night-eating syndrome, on the other hand, had lost comparable amounts of weight without apparent difficulty.

Characteristics of the Illnesses. Although many patients from the special study clinic suffered from long-standing personality disorders, the illnesses to be described were recognized by both the patients and their physicians as discrete reaction patterns different from the usual adjustment of even the most disturbed patients. Despite this they did not fit into any of the conventional diagnostic categories. The predominant symptomatology was depressive, but they were not typical depressions. The closest parallel is perhaps those curious periods of apathy and sadness which occur during the adolescence of schizoid people. Indeed, in their earlier years four of the patients had undergone such illnesses which were not associated with dieting.

In view of the variability of the circumstances in which they occurred it is of interest that these dieting depressions contained enough similar features to warrant the description of a clinical picture. This was manifested in both the interpersonal relations and the symptomatology of the patients. Most of them, for example, had oriented their lives about an intensely ambivalent and dependent relationship with someone who was viewed as the source of all security. The onset of symptoms was usually preceded by a serious disturbance in such a relationship, and it is worthy of note that this disturbance was often initiated by the patient. In some cases it was encouraged by the physician. At this critical time the decision to diet was made. In a companion report evidence is presented that this decision was symbolic of the attempt at emancipation from the dependent relationship, and an act of defiance of the partner [*9*].

The illnesses were remarkably similar from the point of view of symptoms as well as that of interpersonal relations. All contained two distinct phases, characterized respectively by symptoms of anxiety and later by those of depression. In addition, five of the eleven illnesses about which information is adequate were initiated by a period of elation. This elation was generally of mild degree, and was limited for the most part to some overactivity and increased feelings of well-being. During this period none of the patients showed any evidence of disordered thinking or inappropriate behavior, and only one reported any sleep disturbance.

The period of elation appeared to be closely related to the interpersonal considerations which have been described. Thus it began at about the time of the decision to break off an important dependency relationship, and was often first manifested by the feelings of freedom and exultation with which the patient celebrated her apparent release from bondage. These feelings were intensified by the results of the decision to diet. Many of the patients had long cherished secret dreams of the extravagant benefits to be achieved by weight reduction, and when, after years of indecision, they sought to live out this phantasy it was in an atmosphere of excited anticipation. This heightened mood persisted for weeks and even months.

The elation was usually abruptly terminated by a period of anxiety which tended to be of short duration. Some apparently minor incident brought home to the patient the consequences of the course she was following, and she reacted with severe anxiety. During this time she became preoccupied with the danger of living without the support she had so gratuitously cut off, and perhaps more importantly, she began to fear the retaliation of the authority she had defied. Within a week or two this anxiety was displaced by a depressive reaction which lasted for months. During this time the patients showed the typical depressive manifestations of depression of mood, crying spells and sleep disturbance. In each case the disorder was of such severity as to interfere with the ability to work, but retardation was present in only two of the patients. Suicidal ruminations were common but none of the patients made any self-destructive attempts or gestures.

In two of their characteristics these illnesses differed sharply from the clinical picture generally associated with a diagnosis of depression. In the latter condition great importance is traditionally placed upon the expressions of self-condemnation which are considered to arise from the miscarriage of mechanisms of hostility and guilt. It is significant that such attitudes were expressed by only one patient in the course of her dieting depression. Instead, the predomi-

nant complaints were of futility and hopelessness, and the patients were often preoccupied with thoughts of deprivation, not only of food but also of affection and personal interest. Another cardinal sign of textbook descriptions of the depressive reaction is weight loss. It is of interest that these illnesses, initiated by weight reduction, were accompanied in only one instance by further loss of weight. Three patients showed no change in weight, and eight actually gained from 15 to 75 pounds in the course of their illnesses. Table II summarizes this clinical picture of the dieting depression with a list of which features occurred in each patient.

Recovery without apparent residua occurred in all the patients after illnesses which lasted from six weeks to one year. The factors leading to recovery were not clearly defined. Although all the patients discontinued their reducing diets soon after the onset of severe symptoms, increased food intake did not terminate the illnesses. Furthermore, although in each case the disrupted personal relationship was restored, this could as easily have been a result of the recovery as a cause. Several aspects of the problem are illustrated by the history of a patient who was treated for nine months in the special study clinic.

CASE REPORT

M. C., a forty-nine year old housewife, came to the special study clinic with a variety of complaints, most prominent of which were neurodermatitis of twenty years' duration, migraine headaches and generalized aching on the basis of a muscle tension syndrome. She was also found to be overweight (weight, 183 pounds; height, 5 feet 0 inches) but this was not initially a matter of concern to her, nor did she have any clear idea of the duration of her obesity. She had attempted weight reduction only once and had given up after losing 6 pounds.

The patient was a buxom, middle-aged woman with pleasant, even features. She dressed in severe black clothing, seemed tired and discouraged, and spoke in a flat, low, expressionless voice. During her first visit she talked only of her symptoms, and what her many doctors had done for her, and what they had failed to do.

The patient was the second of eleven children of an Italian immigrant family which arrived in this country shortly before her birth. Her parents frequently told her the story of how her mother's milk had given out when the patient was three months old, and since no one in the family knew how to obtain milk in the new country she had been raised on tea. Supposedly as a result of this deprivation she had been a thin, sickly and fearful child. Memories of this period were filled with the picture of a cruel and powerful mother, and later experience contained little to modify this view. Ostensibly because of the mother's need for help with the housework the patient was kept home from school to help her, and thus had little opportunity for contact with her peers. Instead she was occupied with getting her younger siblings ready for school, preparing meals and doing housework which did not end until she had scrubbed the kitchen floor late in the evening. She came to view life then, as unrewarding drudgery in the service of an unpredictable and dangerous tyrant.

She did not remember having thought of rebellion, and instead cherished fantasies of being saved by some outside agency of a power equal to that of her mother. For instance, she recalled with pleasure one occasion when friendly neighbors called the police after her mother had given her a particularly bad beating.

When the patient was sixteen years old her mother arranged a marriage with a neighbor who had taken a fancy to her after seeing her once. She took no part in the arrangements and meekly agreed to her mother's demands. "I didn't know what else to say; I was so young and mother wanted it."

Marriage brought no improvement in her lot. Her husband was a restless, unhappy man who could earn a good living as an auto mechanic but who was rarely satisfied with this. Instead, he frequently quit work to try his hand at other jobs which he felt conferred more prestige, and in these he was usually unsuccessful. From the beginning he was preoccupied with the possibility of his wife's infidelity and jealous of any of her interests outside of him. In an effort to ensure her faithfulness he resorted to a rigid control over her life. He gave her only enough money for the most pressing bills, forbade her to leave the house except to go shopping, and kept her pregnant during many of the early years of their marriage. For a time she struggled against this domination, exploding into screaming temper tantrums or sulking in an exaggerated and histrionic manner. Finally, however, she settled into a grim, depressed mood, martyred and long-suffering. Deciding to "dedicate my life to my (eight) children" she sought to gain a measure of satisfaction by serving them through the compulsive never-ending housework she knew so well. Before she had passed the childbearing age her older children were bringing their babies for her to look after, and as the years went by she found herself becoming even busier. The few intermissions in this life of unrelieved gloom were provided by her frequent and intensely meaningful visits to doctors, visits which apparently fulfilled much the same function as her earlier fantasies of intervention by a benevolent authority.

Treatment lasted nine months during which time the patient was seen two or three times a month for a period of forty-five minutes in duration. Initial con-

tact involved a detailed medical history and physical examination, and medication was frequently prescribed for her many somatic complaints. The patient did not look upon the physician as a psychiatrist, and conceived of the emphasis on her life situation not as a therapeutic instrument but as evidence of the doctor's special interest in her.

The patient's communications were at first limited to tired, repetitious accounts of her many symptoms and her past experiences with doctors. Within two months, however, as she gained confidence in the therapist, she began to speak of her home life and shortly entered with growing enthusiasm into highly dramatic accounts of her sufferings and mistreatment, In the presence of a growing positive transference the patient was able to see that much of her suffering was voluntarily chosen, and she began to explore the possibility of changes in her way of life. During her visits to the clinic particular attention was paid to her inordinate dependence upon her family, and ways in which she might achieve some degree of independence of it. Rather soon she began to refuse excessive demands by her children, and even asked them for help when the housework became too pressing. Furthermore, she began to think of the possibility of recreation away from home, and her old dream of working in a hospital as a nurse's aide was reborn. The therapist actively supported her in these activities, and when her plans ran into the opposition of her family he saw one of her sons to try to persuade him to support his mother's aspirations. One of the most significant therapeutic interventions concerned dieting. Two months after the patient had begun treatment the benefits of weight reduction were discussed and the therapist said that he hoped she would try to lose weight. She reacted with great enthusiasm and began a diet at once which reduced her weight from 183 to 170 pounds in the next two months.

The considerable changes in the patient's living during the early months of treatment were accompanied by a remarkable symptomatic improvement. There was almost complete clearing not only of the depressive and hypochondriacal complaints but also of her neurodermatitis, migraine and muscle tension syndrome. These favorable developments were accompanied by a mood change which at first seemed to be no more than an understandable increase in feelings of well-being. Gradually, however, she became more and more active, began to dress in an extravagant and flamboyant manner, and it was clear that she was becoming elated. This behavior first became manifest at the time that the patient began her weight reduction regimen, and became more prominent following the therapist's talk with her son. Behind it lay a fantasy which she revealed only much later, that the therapist was secretly in love with her. This seemed obvious to her from his disapproval of her mistreatment at the hands of her family, and she felt that sooner or later he would take her away from her unhappy life and marry her. In the fifth month of treatment she put this hope to the test by making frankly erotic overtures to him. He rebuffed these and tried to define the limits of the treatment situation but the patient's expectations could not be bounded by such measures. She left the office perplexed and angry.

The patient broke her next appointment and returned three weeks later profoundly depressed. She reported that following her last visit she had become anxious and agitated, and had cried almost constantly. Sleep was very poor and was frequently disturbed by nightmares of being attacked and robbed. She had been unable to take care of her home, and was both apathetic and retarded. She explained her condition as a perfectly logical reaction to the failure of the therapist to reciprocate her love, and expressed none of the ideas of self-condemnation which would have been expected in a depression of this severity. Unlike the other patients in this group, she was quite anorexic and her weight fell another 25 pounds to a low of 145.

Four months after this exacerbation of symptoms the patient broke off treatment at the special study clinic and information about her thereafter was obtained from the other physicians she consulted. She remained severely depressed for nearly a year. During this time she received intensive psychotherapy from two other psychiatrists and was hospitalized for a course of electroconvulsive therapy, each of which resulted in only temporary alleviation of symptoms. She also sought surgical treatment, and in a six-month period underwent three major operative procedures for cystocele, inguinal hernia and gall stones, all of which had been asymptomatic. Her suffering eventually won the sympathy and concern of her family, and individual members came to treat her with more consideration. Gradually there was a reinstitution of her old hypochondriacal and muscle tension symptoms, a partial clearing of the depressive ones, and the patient was able to return to her former level of adjustment. This was accompanied by a slow increase of her weight to 180 pounds.

COMMENT

This report surely raises more questions than it resolves. For instance, what are the origins of the symptoms reported by the subjects from the nutrition clinic, and by those in the special study clinic? Do the illnesses which occurred in the latter group represent either better documentation or further progression of processes which are common among obese persons during weight reduction regimens? Are these processes primarily physiologic or primarily psychologic in nature, and what are the psychophysiologic interrelations?

The nutrition clinic study provides little evidence upon which to base answers to these

questions. However, the quality of increased irritability suggests that the symptoms may, in part at least, derive from a fundamental property of protoplasm—increased irritability in response to nutritional deprivation.

Such physiologic considerations probably can account only in part for the more serious illnesses which have been described. Characteristics of their symptomatology could not be related to the severity of the nutritional deprivation, whereas they were closely related to specific interpersonal considerations. Indeed, interpersonal factors in the case of M. C. were of such obvious importance as to raise the question of whether or not dieting was of more than incidental significance. Similar doubts could be raised about the role of dieting in all those illnesses which began while the patient was already under treatment; the current enthusiasm for weight reduction makes it unlikely that an obese person could be treated for any length of time for any complaint without being placed on a diet. And the emotional turmoil aroused by other elements of the therapeutic relationship might incorrectly be attributed to this incidental if inevitable prescription.

Although dieting may be merely coincidental with at least those illnesses which began during treatment, the testimony of the patients does not support this view. None of them looked upon weight reduction in any casual terms, and for the majority it had a significance far beyond that of a simple loss of weight. It involved primitive, undifferentiated issues of power and control, dependence and freedom, and the affective quality of the self image. In the light of this testimony, a possible role of dieting in the precipitation of severe emotional disorders suggests itself. For some obese persons a determined decision to diet may emerge only from a conflict of the intensity necessary to raise these issues; it may be possible to resolve such a conflict only in psychotic terms.

TREATMENT AND PROPHYLAXIS

Once the patient manifests psychotic symptoms her treatment properly becomes the responsibility of the psychiatrist. Furthermore, before the initiation of a weight reduction program psychiatric consultation might well be a routine procedure for any obese person who has undergone a previous psychosis, especially if this were related to an attempt at dieting. However, as has been noted, half of all obese persons experience untoward symptoms during weight reduction regimens, and most of these patients must be cared for by internists and general practitioners. Since successful management of attempts at weight reduction helps prevent the more severe disorders it may be appropriate to consider certain aspects of the care of obese patients.

Experience in the special study clinic indicates that the patient's relationship with her physician may play an important role in the precipitation of a dieting depression. Paradoxically, such an outcome may be more frequent among the patients of physicians who concern themselves with the emotional problems of their patients than among those who prescribe weight reduction programs mechanically and with little prospect of serious cooperation by the patient. This derives in part from the greater effort at dieting which may be exerted by the patient who enjoys a better relationship with her physician. But it may also result from the physician's greater awareness of the difficulties in the patient's life situation, and his consequently greater inclination to help the patient make favorable changes. It is only too easy to agree with the patient's desire to emancipate herself from a relationship of morbid dependency upon an exploiting and manipulative authority. And yet, if a major precipitating circumstance in these illnesses is the premature disturbance of an intense dependency relationship, such a step may well encourage the patient to exert herself beyond her adaptive capacities. If the physician at the same time collaborates in an attempt at weight reduction, it provides the ingredients we have noted as specific for a dieting depression.

It is important for the physician dealing with obese patients to bear in mind the relative ineffectiveness of current measures of treatment, the suffering and hazards they entail, and the remarkably poor results of long term follow-up. He must learn what unrealistic expectations the patient has in regard to weight reduction and help her to keep it in perspective as a hygienic measure of certain limited usefulness which will not guarantee happiness. Management of such a patient may require careful assessment of her interpersonal capabilities, particularly of the ability to survive without the support of her main dependency relation, morbid as it may be.

If he will really serve his patient's needs the physician must keep in mind the obese person's very real vulnerabilities, and he will restrain her from attempting prematurely either a reducing

regimen or the psychodynamically related separation from an object of intense dependency. For, until the patient has developed the tools necessary for independent living, such attempts may be as dangerous as they are ineffective.

SUMMARY AND CONCLUSIONS

1. One hundred consecutive obese persons admitted to a nutrition clinic were questioned as to their tolerance of previous weight reduction regimens. Of the seventy-two patients who had attempted dieting 54 per cent reported that such attempts had been associated with untoward emotional reactions.

2. Of twenty-five obese persons referred to a special study clinic nine experienced severe emotional disorders during attempts at weight reduction.

3. These dieting depressions were characterized by a short period of intense anxiety followed by a prolonged period of depression. These symptoms were often preceded by a period of elation during which the decision to diet was made.

4. During these illnesses the patients experienced a profound disturbance in a major dependency relationship which was psychodynamically related to the attempt at weight reduction.

5. These findings emphasize the vulnerability of obese persons during attempts at weight reduction and suggest that reducing diets should be prescribed only after careful evaluation of the patient's past and present life adjustment.

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Cardiac Involvement in Coccidioidomycosis*

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IT has been stated [*1*] that "almost all of the microorganisms are capable at times of producing . . . myocardial lesions . . . due either to the presence of these organisms or to toxic or metabolic disturbances caused by the infection. . . . In almost all of the . . . infections [other than diphtheria] evidence of cardiac involvement consists either of electrocardiographic changes which are usually non-specific and transient or of relatively mild and non-specific myocardial lesions which are found in fatal cases."

Myocardial involvement has been reported in a variety of fungus diseases [*2*]. In those due to actinomycosis, congestive heart failure was the most common clinical manifestation. In a study [*3*] of myocarditis in acute infectious diseases, however, congestive heart failure was found to be uncommon, although abnormal electrocardiograms, chiefly abnormal T waves; were noted in one-third of all patients. The clinical manifestations, in the order of their diagnostic importance in these cases, were: an apical heart sound of poor quality, drop in systolic blood pressure of 20 mm. or more, gallop rhythm, systolic murmur and pulse over 125.

From 6,000 clinically recognizable cases of coccidioidomycosis which occurred in members of the Armed Forces from 1941 to 1946, ninety-five cases with disseminated coccidioidomycosis were accumulated by the Army Institute of Pathology [*4*]. Initiating signs and symptoms, general symptomatology and physical findings were tabulated for the group. The only symptom reported which might have been referable to heart disease was dyspnea. This was present in twelve of the ninety-five patients. Whether or not any of these twelve patients with dyspnea had cardiac involvement at autopsy was not indicated.

A survey of the electrocardiograms of twenty patients with primary pulmonary coccidioidomycosis revealed inversion of T waves and/or low voltage of all complexes in five patients during the illness [*5*]. There was reversion to upright T waves and normal amplitudes after recovery.

Clinical cardiac involvement due to coccidioidomycosis has been reported in only six patients to the present time, all of whom had clinical pericarditis [*6,7*]. Neither myocarditis nor endocarditis due to coccidioidomycosis has been recognized clinically but have been reported as autopsy observations [*4,6,8–15*].

Pericarditis, in the reported cases [*6,7*], caused substernal chest pain, a pericardial friction rub, pericardial effusion and elevation of the S-T segments in the electrocardiogram. Autopsies were not reported in these cases. None of the reported patients with autopsy findings of pericarditis due to coccidioidomycosis were said to have had clinical signs or symptoms of pericarditis.

Clinical Data of the Present Study. The records of twenty-two patients with coccidioidomycosis on whom autopsies were performed at this hospital were reviewed for symptoms, signs, x-ray findings and electrocardiographic abnormalities suggestive of cardiac disease. The clinical data on these patients are summarized in Table 1. This group included fifteen cases of disseminated coccidioidomycosis, two cases of direct extrapulmonary extension of coccidioidomycosis, and five cases in which asymptomatic quiescent localized coccidioidal granulomas were found incidentally at autopsy. All were men, ranging in age from twenty-three to seventy-nine years. Of the seventeen patients with active disseminated coccidioidomycosis there were nine Negroes, two Mexicans, three Filipinos and only three Caucasians, whereas the five patients in whom asymptomatic coccidioidal granulomas were found at autopsy were all Caucasian. These patients were known to have had their

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TABLE I

CLINICAL AND PATHOLOGIC DATA OF PATIENTS WITH COCCIDIOIDOMYCOSIS AT AUTOPSY

Case	Clinical Data										Pathologic Data	
							Heart				Diagnoses	
	Clinical Diagnosis	Age (yr.)	Race	Sex	Duration of Disease (mo.)	Other Diagnoses	Symptoms (duration in days)	Electrocardiogram	X-ray	Degree*	Major	Other
	Disseminated coccidioidomycosis with:											
1	Subcutaneous abscesses	44	Y	M	3	0	Orthopnea—90†	Low and ↓ T	Enlarged ?, effusion ?	3	Disseminated coccidioidomycosis	0
2	Subcutaneous abscesses, meningitis	25	N	M	60‡	0	0	0	Normal	1	"	0
3	Pneumonia	53	N	M	3	0	Dyspnea—2†	0	Normal	3	"	0
4	Spinal cord compression	63	W	M	9	0	0	Normal	Normal	1	"	0
5	Meningitis	31	W	M	4	0	0	0	Normal	0	"	Carcinoid
6	Spinal cord compression	23	N	M	12	0	0	0	Normal	?	"	0
7	Subcutaneous abscesses	51	N	M	3	0	Dyspnea, orthopnea, chest pain—6†	0	Normal	3	"	0
8	Subcutaneous abscesses	29	N	M	18	Diabetes	0	Normal	Normal	1	"	0
9	Subcutaneous abscesses	31	N	M	12	0	0	0	Normal	0	"	0
10	Pneumonia, meningitis	30	W	M	6?	Myocarditis (etiol. ?)	Dyspnea, orthopnea, edema—240†	Low and ↓ T	Enlarged	2	"	Myocarditis, fibroelastosis of heart
11	Pneumonia, meningitis	56	Y	M	5	0	0	0	Normal	1	"	Generalized arteriosclerosis
12	Meningitis	30	W	M	17	0	0	0	Normal	1	"	0
13	Meningitis	45	N	M	5	0	0	0	Normal	1	"	Chronic pyelonephritis Generalized arteriosclerosis
14	Meningitis	42	W	M	4	0	0	0	Normal	1	"	Amyloidosis
	Direct extrapulmonary extension of coccidioidomycosis:										Coccidioidomycoses with extension to:	
15	Mediastinitis adenopathy	41	N	M	8	Myeloid leukemia	Dyspnea, orthopnea edema—14†	Normal	Normal	2	Neck, liver and mediastinum	Myeloid leukemia
16	Pneumonia, pericardial effusion	48	Y	M	16	0	Dyspnea, orthopnea, chest pain—480†	↑ ST, ↓ T	Enlarged ?, effusion ?	3	Heart	0
	Other:											
17	Bronchopneumonia	35	N	M	2	Diabetes	0	0	Normal	1	Disseminated coccidioidomycosis	0
18	Uremia	29	W	M	?	0	0	Left ventricular hypertrophy	Enlarged	1	Chronic nephritis	Disseminated coccidioidomycosis
19	Cerebral hemorrhage	79	W	M	?	Arteriosclerotic heart disease	0	Infarct	Normal	0	Arteriosclerotic heart disease	Coccidioidomycosis adrenal
20	Carcinoma of pancreas	41	W	M	?	0	0	Ischemia	Normal	1	Cancer of pancreas	Coccidioma lung
21	Myocardial infarction	58	W	M	?	0	Chest pain—1	Infarct	Normal	0	Arteriosclerotic heart disease	Coccidioma lung
22	Myocardial infarction	42	W	M	?	0	Chest pain—1	Infarct	Normal	0	Arteriosclerotic heart disease	Coccidioma lung

* Degree of pathologic cardiac involvement:
3—Carditis, severe, with coccidioidal spherules
2—Pancarditis, severe, without coccidioidal spherules
1—Non-specific scarifying or inflammatory lesions
0—No lesions (other than those of arteriosclerosis)

† See clinical summaries.

‡ The onset of the coccidioidal infection in this case is uncertain, the patient having had fever and sweating for 5 years, and subcutaneous nodules for 9 months.

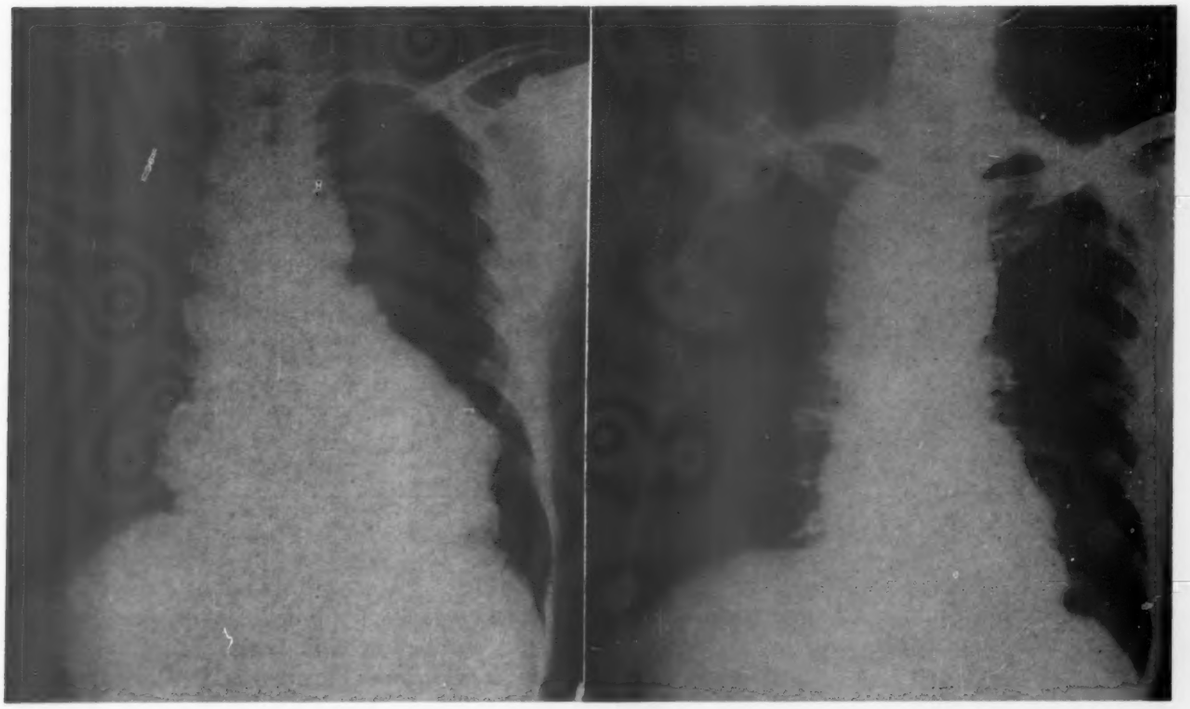


FIG. 1. Case 1. X-rays of the chest demonstrate a reduction in size of the cardiac silhouette between September 14, 1949, (A) and October 5, 1949, (B). A pericardial effusion was suspected at fluoroscopy, at the time of the first x-ray. A coccidioidal pericarditis was present at autopsy.

infection for periods ranging from two months to five years, with an average of eight months, prior to death.

Of the twenty-two patients, six had symptoms and/or signs suggestive of heart disease, with no etiology other than coccidioidomycosis apparent for such heart disease. Each of these six patients was found to have an inflammatory process present in one or more layers of the heart. Coccidioidal spherules were demonstrated in the hearts of four, chronic non-specific inflammatory lesions were found in all layers of the heart in the other two. A summary of each of these six cases is presented subsequently.

Dyspnea and/or orthopnea was present in each of these six patients, and in no others. The absence of dyspnea and orthopnea in other patients with equally severe lung disease but without pathologic cardiac involvement would suggest that these symptoms were referable to the heart.

Every patient with pericarditis who subsequently was found to have coccidioidal organisms in the pericardium (Cases 1, 7 and 16) had symptoms suggestive of pericarditis. These included dyspnea, orthopnea and/or chest pain. Two of the three had signs suggestive of pericarditis or pericardial effusion, including an enlarged cardiac silhouette, a weak cardiac pulsation at the time of fluoroscopy, slight S-T segment elevation on the electrocardiogram, a weak radial pulse, tachycardia and cyanosis. The enlarged cardiac silhouette in one patient decreased markedly within three weeks. (Fig. 1.) These three patients are the first to be reported with clinical evidence of pericarditis, confirmed by autopsy.

Myocarditis, present in all six patients, could have been one of the causes of dyspnea, orthopnea, ankle edema, cardiomegaly, tachycardia, cyanosis and electrocardiographic changes. In Case 10, the patient was admitted to the hospital with signs and symptoms of a myocarditis.

Enlargement of the cardiac silhouette on x-ray was present in four of the twenty-two patients. This was apparently due to pericardial effusion in Cases 1 (Fig. 1) and 16. It is believed that the cardiomegaly in Case 10 was due to myocarditis. Cardiomegaly in the fourth patient, Case 18, was due to hypertension.

Electrocardiograms were available in eleven of the twenty-two cases. Of these, eight were abnormal. Elevated S-T segments and inverted T waves were present in Case 16. In this case an

TABLE II

CORRELATION OF CARDIAC SYMPTOMS AND PATHOLOGIC LESIONS IN DISSEMINATED COCCIDIOIDOMYCOSIS

Cases	Degree of Pathologic Cardiac Involvement *	Duration of Cardiac Symptoms	"Age" and Type of Pathologic Cardiac Lesions
Case 3.....	3	2 days	Acute and subacute granulomas in myocardium
Case 7.....	3	6 days	Subacute granulomatous pericarditis with myocardial and epicardial lesions
Case 15....	2	2 wk.	Chronic smoldering non-specific pancarditis
Case 1.....	3	3 mo.	Chronic scarifying granulomatous pericarditis and myocarditis
Case 10....	2	8 mo.	Chronic scarifying non-specific pancarditis
Case 16....	3	16 mo.	Chronic and acute granulomatous pericarditis and myocarditis
9 Cases.....	1	None	Chronic non-specific scarifying or inflammatory lesions
3 Cases.....	0	None†	.....
1 Case.....	?	None	.....

* See Table I.

† Other than chest pain due to myocardial infarction.

acute and chronic suppurative pericarditis due to Coccidioides immitis was found. Low T waves were present in Case 1, associated with roentgenographic evidence of a pericardial effusion. The T waves in this patient became taller upon disappearance of the effusion. Low and inverted T waves were present in Case 10. In this patient a non-specific myocarditis was found. Abnormalities in the other five patients were due to arteriosclerotic heart disease, hypertension or anoxia secondary to shock.

Table II demonstrates the correlation between the presence of cardiac symptoms and the extent of cardiac involvement at autopsy. Comparison of the duration of cardiac symptoms and the "age" of the microscopic lesions in the heart reveals a distinct correlation.

It is apparent that the cardiac signs and/or symptoms in these six cases reflected the presence of an active carditis in every instance, spherules being demonstrable in the cardiac lesions of four and a non-specific inflammatory process in all layers of the heart in two. It is of interest that of the fourteen patients without signs or symptoms suggestive of heart disease six exhibited no inflammatory disease and eight showed merely chronic non-specific inflammatory disease in the heart. In the latter group, epicarditis (interstitial lesions of the visceral pericardium) alone was found in three patients, epicarditis and myocarditis in two, epicarditis and mural endocarditis in one, and myocarditis alone in two. The lesions found within the hearts of these eight patients were morphologically similar to the non-specific inflammatory lesions found in those with clinically manifest cardiac disease. The lesions in the former cases, however, were smaller in size and fewer in number. No more than two cardiac layers were involved in these instances.

The specific and non-specific cardiac lesions are recorded in Table III. It may be concluded that one-third of the patients with disseminated coccidioidomycosis exhibited clinical signs of heart disease. All of these had cardiac inflammatory lesions. (Table II.) Of those patients with disseminated coccidioidomycosis without clinical heart disease one-half showed inflammatory lesions in one or more layers of the heart. (Table II.)

CASE REPORTS

CASE 1. This forty-four year old Filipino man was a laborer. He was admitted on September 8, 1949, complaining of productive cough, fever, papular skin lesions and orthopnea during the month prior to admission. Examination revealed a temperature of 101.4°F., a pulse of 110 per minute and a blood pressure of 100/84. A smear of one of the skin lesions revealed C. immitis spherules. An x-ray of the chest disclosed marked cardiac enlargement suggestive of pericardial effusion, miliary pulmonary infiltration and hilar adenopathy. (Fig. 1.) At fluoroscopy, the cardiac pulsation was weak. Coccidioidal pericarditis with effusion was suspected. An electrocardiogram revealed low T waves in all leads and a sinus tachycardia. On October 5 the heart size on x-ray was normal. (Fig. 1.) The T waves were taller on October 14. Fever and tachycardia persisted. Dyspnea and

TABLE III

CARDIAC PATHOLOGY IN C. IMMITIS INFECTION

Case	Coccidioidomycotic Carditis					Non-specific Carditis					Aschoff-like Myocarditis	Miscellaneous Findings
	Pericarditis G. M.*	Epicarditis G. M.	Myocarditis G. M.	Mural Endocarditis G. M.	Valves	Pericarditis	Epicarditis	Myocarditis	Mural Endocarditis	Valves		
1	X X	X X	X X	..	..	..	..	X	..	..	X	.....
2	.....	.....	.....	..	..	..	..	X	..	..	..	Interstitial fibrosis
3	.....	.....	X	..	..	..	..	X	..	..	X	.....
4	.....	.....	.....	..	..	..	X	X	..	..	..	.....
5	.....	.....	.....	..	..	..	..	..	..	..	..	.....
6	.....	.....	.....	..	..	..	..	..	..	..	..	.....
7	X X	X X	X X	..	..	..	..	X	X	..	..	Endocardial fibrosis
8	.....	.....	.....	..	..	..	..	..	..	..	..	Perivascular fibrosis
9	.....	.....	.....	..	..	..	..	..	..	..	..	.....
10	.....	.....	.....	..	..	..	X	X	X	..	..	Perivascular and endocardial fibrosis
11	.....	.....	.....	..	..	..	X	..	..	..	..	Epicardial and perivascular fibrosis
12	.....	.....	.....	..	..	..	..	..	..	..	..	Perivascular fibrosis
13	.....	.....	.....	..	..	..	X	X	..	..	..	Perivascular fibrosis
14	.....	.....	.....	..	..	..	..	..	..	..	..	Perivascular fibrosis
15	.....	.....	.....	..	..	..	X	X	X	..	..	Endocardial fibrosis
16	X †	X †	X †	..	..	..	..	..	..	..	..	.....
17	.....	.....	.....	..	..	..	..	X	..	..	?	.....
18	.....	.....	.....	..	..	..	X	..	..	..	..	Interstitial fibrosis
19	.....	.....	.....	..	..	..	X	..	X	..	..	Recent and old infarcts
20	.....	.....	.....	..	..	..	X	..	..	..	..	Endocardial and perivascular fibrosis
21	.....	.....	.....	..	..	..	..	..	..	..	..	Recent and old infarcts
22	.....	.....	.....	..	..	..	..	..	..	..	..	Recent and old infarcts

* G—Grossly observed.
M—Microscopic findings
† Inadequate slide preparations

cyanosis were present for two days prior to his death on November 14, 1949.

Autopsy revealed an obliterative chronic scarifying granulomatous pericarditis and both non-specific and granulomatous lesions in the myocardium. Spherules of C. immitis were found within the pericardial and myocardial lesions. These lesions were readily apparent grossly and microscopically.

Comment: Coccidioidal pericarditis with effusion was probably present on admission, causing the orthopnea noted at that time. The effusion disappeared by the end of the first month of hospitalization. The terminal dyspnea and cyanosis may have been related to his myocarditis and pericarditis.

CASE 16. This forty-eight year old Filipino man was a farmer. He was admitted on November 16, 1944, with the chief complaints of cough, chest pain, chills, fever, night sweats, weight loss, dyspnea and orthopnea of two months' duration. Examination revealed a temperature of 102°F., a pulse of 120 per minute and a blood pressure of 110/70. An x-ray of the chest revealed a large cardiac silhouette and pneumonia. A coccidioidin skin test was strongly positive. The heart size returned to normal in a month; fever, tachycardia and tachypnea gradually decreased, and he was discharged on May 4, 1945. In November, 1945, he noted the onset of nocturnal chest pain, described as "a heavy feeling with a sensation of constriction." On readmission on December 31, 1945, examination revealed a temperature of 101.4°F, a pulse of 112 per minute and a blood pressure of 116/80. The patient was dyspneic and cyanotic. An x-ray of the chest again revealed marked cardiac enlargement and pneumonia. An electrocardiogram on January 9 showed slight elevation of the S-T segments in leads I, II and III, and an inverted T wave in lead CF 4, consistent with pericarditis. Terminally, he became more dyspneic and cyanotic, the temperature, pulse and respiratory rate gradually rising. He died on January 17, 1946.

Autopsy revealed an acute and chronic suppurative pericarditis due to C. immitis, with invasion of the left ventricular wall.

Comment: It appears that coccidioidal pericarditis with effusion was present during his first admission, causing the orthopnea and the cardiomegaly, and that pericarditis was present during his second admission, causing the chest pain, dyspnea and cyanosis.

CASE 7. This fifty-two year old Negro man was a laborer. He was admitted on March 17, 1947, with a history of draining subcutaneous nodules, a large tender mass in the right supraclavicular region, and a slight cough of three months' duration. Examination

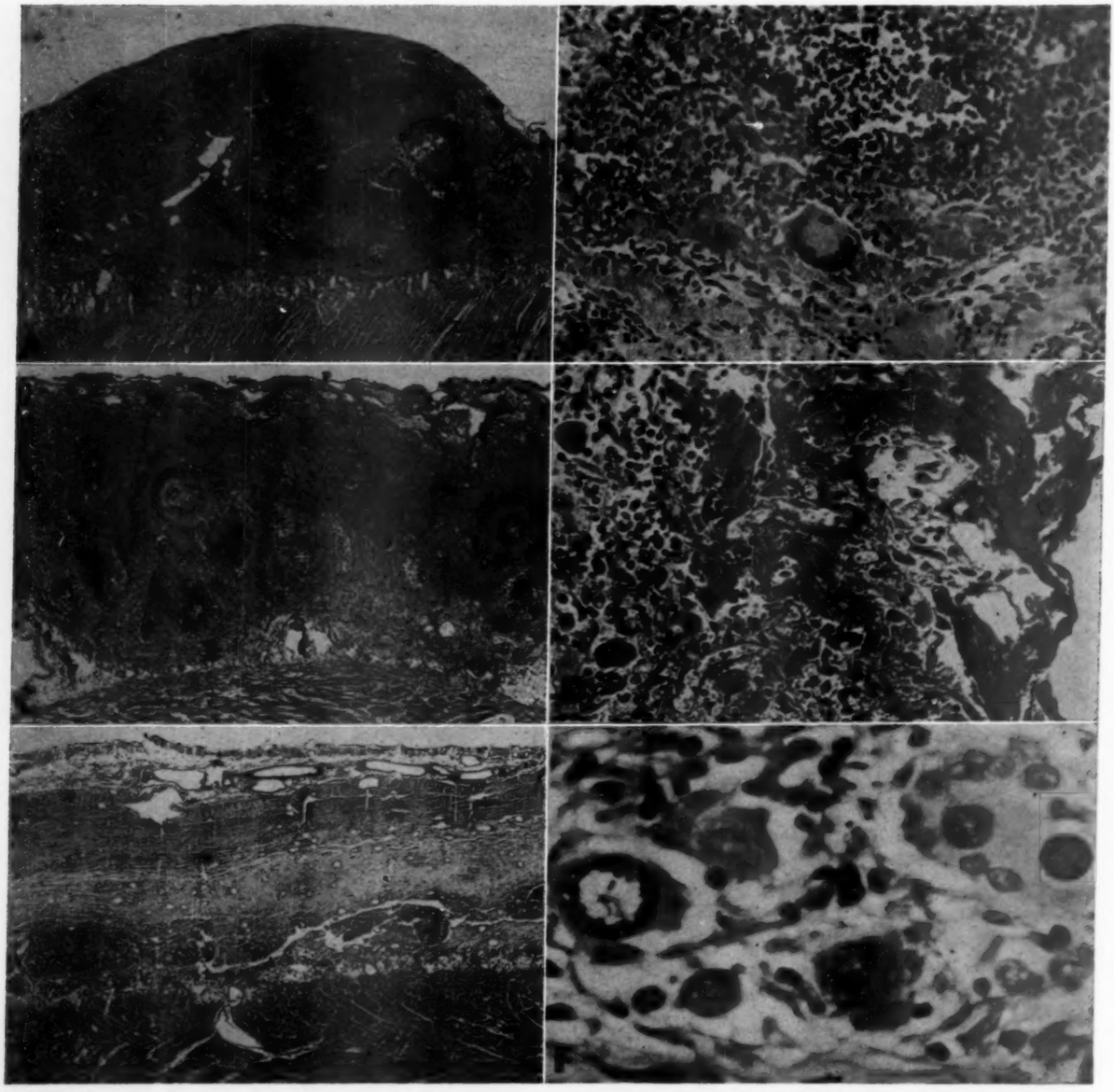


FIG. 2. A, Case 7. Nodular coccidioidomycotic, granulomatous epicarditis with multicentric abscesses. There is a diffuse chronic scarifying, non-specific, inflammatory reaction showing a surface fibrinous pericardial exudate and sharp demarcation from the underlying myocardium. Hematoxylin and eosin; original magnification, × 40. B, same case. Focal epicardial abscess containing a spherule of Coccidioides immitis, surrounded by a scarifying, chronic non-specific, process containing lymphocytes, fibroblasts, occasional plasma cells and multinucleated giant cells. Hematoxylin and eosin; original magnification, × 120, high power of A. C, same case. Diffuse scarifying coccidioidomycotic granulomatous epicarditis with multicentric abscesses. There is a thick fibrinous, non-adhesive surface reaction and sharp demarcation from the underlying myocardium. Hematoxylin and eosin; original magnification, × 40. D, same case. Organizing fibrinous pericarditis with underlying chronic non-specific epicarditis containing lymphocytes, plasma cells, dilated capillaries and both uni- and multinucleated histiocytes. Hematoxylin and eosin; original magnification, × 120, high power of C. E, Case 1. Chronic scarifying, diffusely adherent and obliterative, granulomatous coccidioidomycotic epicarditis and pericarditis with residual pericardial slits. Note the density of the parietal pericardial, laminated, fibrous connective tissue and sharp demarcation from the underlying myocardium. Hematoxylin and eosin; original magnification, × 40. F, same case. Numerous spherules of C. immitis inside and outside of multinucleated giant cells. There is a delicate fibrillar connective tissue deposit stippled with lympocytes. Giemsa; original magnification, × 120, high power of E.

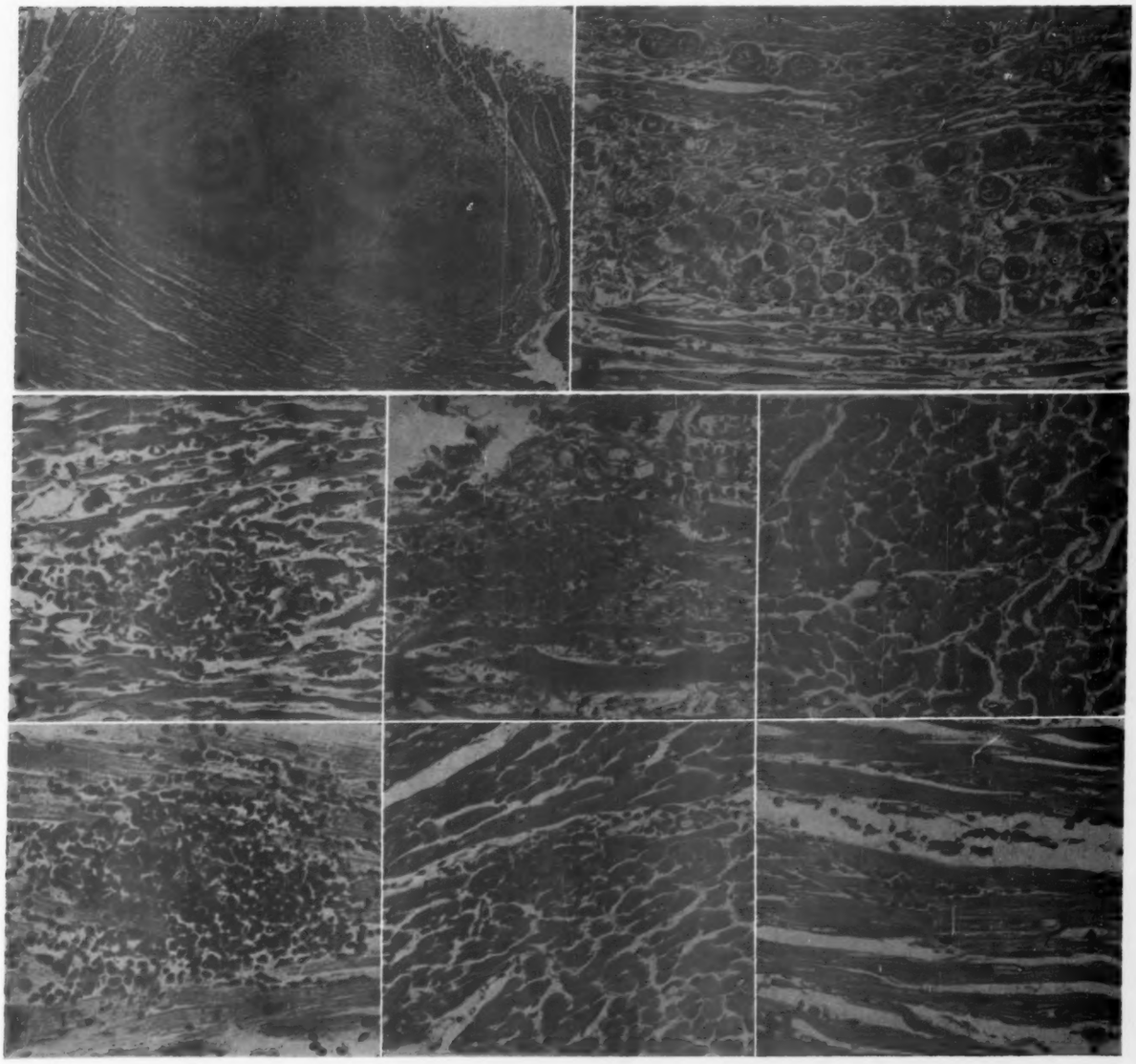
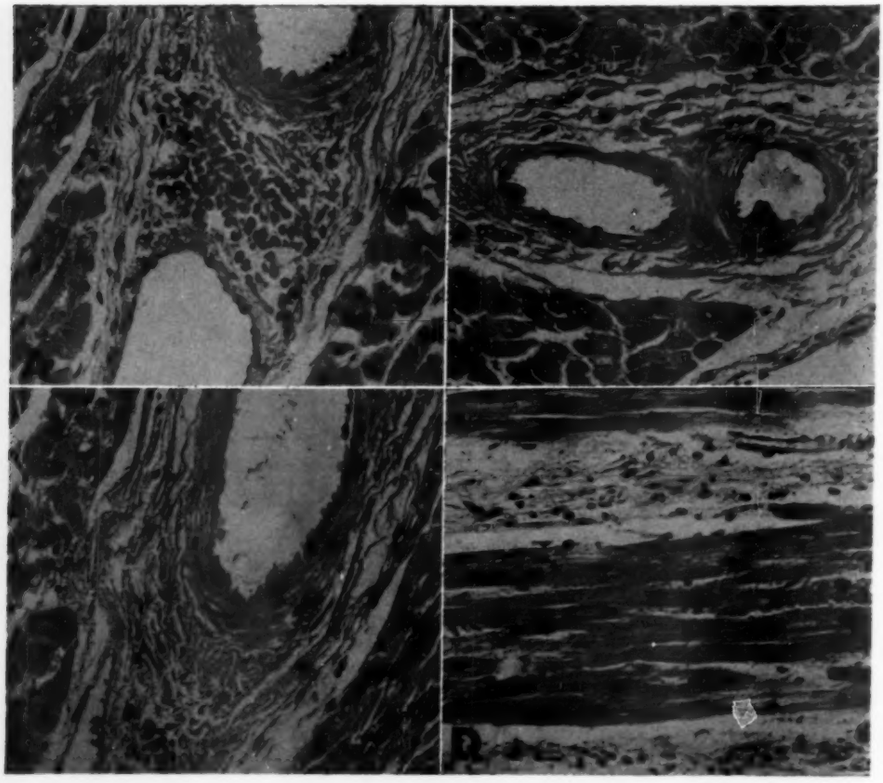


FIG. 3. A, Case 1. Oval caseous coccidioidomycotic granuloma with central necrosis and marginally scalloped, granulation tissue. Note the peripheral compression of the surrounding myocardium. Hematoxylin and eosin; original magnification, × 40. B, same case. Innumerable spherules of C. immitis in scar tissue containing occasional plasma cells and lymphocytes. high power of A. C, same case. Spherule of C. immitis in a fusiform infiltrate of lymphocytes and plasma cells. There is an associated myocardial fiber degeneration and delicate deposit of smudgy fibrillar connective tissue. D, Case 7. Spherule of C. immitis in a fusiform exudate similar to that seen in C, in a subepicardial position (involvement by extension). E, same case. Spherule of C. immitis, showing necrobiosis, associated only with interstitial lymphocytes. F, Case 1. Severe exudative fusiform inflammatory reaction consisting of lymphocytes and plasma cells, showing delicate granular and fibrillar central smudginess in the absence of visible spherules. G, Case 3. Ovoid focus of fibroblasts and lymphocytes and an interstitial septum stippled by lymphocytes. No spherules were demonstrable. H, Case 4. Interstitial lymphocytes, focally clustered. Microphotographs B through H: hematoxylin and eosin, original magnification, × 120.

revealed a temperature of 100.2°F., a pulse of 84 per minute and a blood pressure of 120/85. An x-ray of the chest revealed right upper lobe infiltration. C. immitis spherules were demonstrated in the drainage from one of the lesions and in the sputum. Marked tachycardia and fever persisted. During the last six days prior to death he had severe chest pain, dyspnea and orthopnea. He died on April 3, 1947.

Autopsy revealed 800 cc. of blood tinged pericardial fluid, an organizing hemorrhagic pseudomembranous granulomatous pericarditis and epicarditis, and a superficial granulomatous myocarditis due to C.



FIGS. 4A–D. A, Case 15. Paravascular lymphocytes and plasma cells without altered interstitial collagen. B, Case 3. Paravascular, fusiform-shaped, Aschoff-like granulomas consisting of lymphocytes, Anitschkow myocytes, associated with swollen collagen fibers and perivascular fibrosis. C, Case 15. Perivascular mature hyaline fibrillar connective tissue. D, Case 2. Interstitial fibrosis containing occasional lymphocytes. Note the occasional myocardial fiber exhibiting granular degenerative changes. All microphotographs: hematoxylin and eosin, × 120.

immitis. There was a fairly marked left ventricular endocardial fibrosis and acute cor pulmonale.

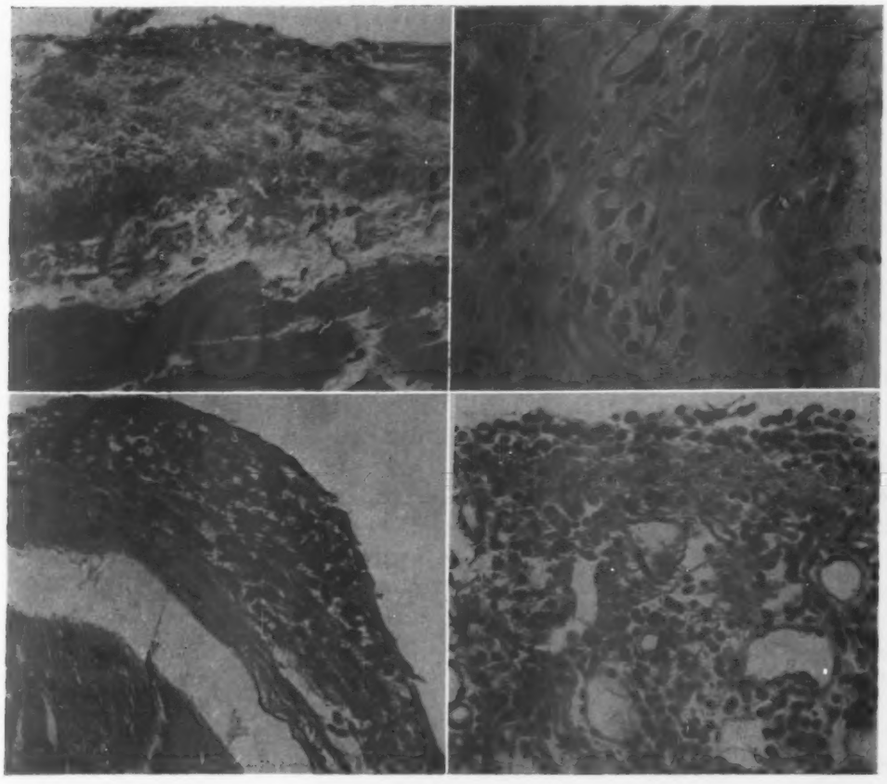
Comment: This patient's terminal symptoms of chest pain, dyspnea and orthopnea were probably due to pericarditis, pericardial effusion and myocarditis.

CASE 15. This forty-one year old Negro man was a street maintenance worker who was admitted on December 10, 1952, with a history of a tender mass over the upper sternum, fatigue, anorexia, fever, chills, sweating, dysphagia and weight loss of three months' duration. Examination revealed a temperature of 99°F., a pulse of 90 per minute and a blood pressure of 95/65. X-rays of the chest disclosed a large mass in the upper anterior mediastinum and bilateral upper lobe infiltrations. Examination of the peripheral blood and bone marrow indicated the presence of subacute myelogenous leukemia. C. immitis was cultured from the sternal lesion. Complement fixation for coccidioidomycosis was 4 plus at a dilution of 1:512. Severe dyspnea, orthopnea and ankle edema developed during the final two weeks. He died on April 16, 1953.

Autopsy revealed a non-specific epicarditis, myocarditis and mural endocarditis. Foci of endocardial fibrosis were found in the left ventricle. The parietal pericardium was greatly thickened and adherent to the pleura.

Comment: This patient's dyspnea, orthopnea and ankle edema were probably due in part to the myocarditis. Whether or not the thickened parietal pericardium contributed to the clinical findings is difficult to determine.

CASE 3. This fifty-three year old Negro man was a furniture upholsterer who was admitted on January 22, 1952, with a history of headaches, arthralgia, fever and cough of two months' duration. Examination revealed a temperature of 99°F., a pulse of 88 per minute and a blood pressure of 150/90. X-rays of the chest showed increasing miliary pulmonary infiltrations. C. immitis was cultured from the blood and sputum. The complement fixation test for coccidioidomycosis was 4 plus at a dilution of 1:64; the precipitin titer was 4 plus at 1:10. A coccidioidin skin test was negative at 1:100. Fever, tachycardia and tachypnea persisted throughout his hospitalization. Dyspnea was



FIGS. 4E–H. E, Case 7. Subendocardial fibrosis with superficial fusiform subendothelial infiltration of lymphocytes. F, Case 11. Epicardial fibrosis with interstitial lymphocytes, monocytes, plasma cells and histiocytes. G, Case 15. Fusiform subendocardial deposits of lymphocytes in a delicate reticular connective tissue. H, same case. Diffuse infiltration of epicardium by lymphocytes and plasma cells, associated with a band-like surface fibrosis and ectasia of interstitial blood vessels. All photomicrographs: hematoxylin and eosin, × 120.

present for two days prior to death. He died on February 21, 1952.

Autopsy revealed an extensive non-specific and granulomatous myocarditis. This was not apparent grossly.

Comment: This patient's terminal dyspnea may or may not have been related to his myocarditis.

CASE 10. This thirty year old Mexican man was a laborer who was admitted on September 19, 1953. Cough and exertional dyspnea began in July, 1953, and orthopnea and ankle edema in August. Hemoptysis and fever were present for two days prior to admission. The patient lived in the San Fernando Valley, and had visited the San Joaquin Valley in August, both endemic areas of coccidioidomycosis. Examination revealed a temperature of 101°F., a pulse of 130 per minute and a blood pressure of 96/74. Cardiomegaly, a gallop rhythm, hepatomegaly and ankle edema were present. The venous pressure was elevated and the circulation time prolonged. An electrocardiogram revealed a sinus tachycardia, low and inverted T waves. An x-ray of the chest demonstrated cardiomegaly and a left lower lobe infiltrate. Pleuritic pain developed over the pulmonary infiltrate soon after entry. Fever, tachycardia and borderline congestive failure persisted. Coccidioidin skin tests were 2 plus in a dilution of 1:100 on October 9, 1953, and negative on January 22, 1954. Coccidioidal complement fixation and precipitin tests were negative on October 15, 1953. On January 11, 1954, the complement fixation titer was 2 plus at 1:8, the precipitin titer was 2 plus at 1:10. The complement fixation titer persisted. The precipitin test was negative on February 25, 1954. C. immitis was cultured from the sputum. Symptoms of meningitis were first apparent on February 21, 1954, progressing to his death on March 12, 1954.

Autopsy revealed cardiomegaly, non-specific epicarditis, myocarditis and mural endocarditis and extensive subendocardial fibroelastosis of the left ventricle. A moderate amount of perivascular fibrosis was found within the myocardium.

Comment: Although this patient had symptoms and signs of a myocarditis prior to the appearance of clear-cut evidence of his pulmonary infection, coccidioidal myocarditis may have been present.

PATHOLOGIC OBSERVATIONS

Review of the Literature. Changes in the heart due to coccidioidomycosis have been reported chiefly from autopsy observations. Of the fifty autopsy cases of disseminated coccidioidomycosis accumulated by the Army Institute of Pathology [*4*], the myocardium was involved in fourteen. Five of these showed both gross and microscopic lesions whereas nine were identified by microscopic studies alone. In seven of these fourteen cases, simultaneous lesions of the pericardium were evident. Within the myocardium there were infrequent miliary granulomatous lesions. Though not specifically stated, the lesions apparently contained the specific spherules of C. immitis. The myocardium was noted to be the eleventh structure in frequency of involvement, the lungs, lymph nodes, spleen, skin, kidney, liver, pleura, bones, meninges and adrenal glands preceding it, in that order. In 1947 Gore and Saphir [*8*] reviewed 1,402 cases of myocarditis encountered in the autopsy files of the Army Institute of Pathology. In eleven of these the inflammatory process was recorded as due to coccidioidomycosis. Reingold [*9*] in 1950 reported four cases of coccidioidomycosis with cardiac findings at autopsy. In two of these cases non-specific, monocytic, lymphocytic, polymorphonuclear leukocytic interstitial and perivascular infiltration of cells were noted and in one instance the cellular infiltrate consisted of eosinophilic and polymorphonuclear leukocytes. This was regularly associated with edema and degenerative changes of the cardiac fibers adjacent to these foci, characterized by indistinct striations and pyknotic nuclei. In the fourth case tiny tubercles were visible grossly in the left ventricular myocardium. These miliary foci consisted of anuclear necrosis, marginated by monocytes and lymphocytes, as well as multinucleate giant cells, and contained the spherules of C. immitis. Lee [*6*] in 1944 reported finding the specific spherules of this disease between the cardiac muscle fibers in three patients, one of whom showed an associated myocardial "cold abscess." Hentel et al. [*10*] reported an instance of scattered grayish coccidioidal granulomata measuring up to 0.5 cm. within the heart, without presenting further details. Maloney [*11*] in 1952 briefly recorded an autopsy performed for this disease wherein the heart showed "numerous areas of interstitial edema within which there were occasional small numbers of round cells, rare polymorphonuclear leukocytes, and occasional Anitschkow myocytes." This was called a "subacute myocarditis."

The pericardium was involved by C. immitis in seven of the fifty autopsies reported from the Army Institute of Pathology in 1946 [*4*]. The pericardium was listed as the sixteenth structure in frequency of involvement. It was considered that the pericardium was not primarily involved by metastases or extension from the lung or pleura, but that pericardial involvement was due to eruption of a superficial lesion located within or just beneath the epicardium. Serofibrinous pericardial effusion, as well as fibrous adhesive pericarditis with foci of necrosis simulating caseation, were observed in this series. Evans and Ball [*12*] in 1929 recorded one instance of granulomatous pericarditis in eighteen autopsied patients with coccidioidomycosis. A patient reported by Larson and Scherb [*7*] in 1953 was found at autopsy to have a diffuse fibrous adhesive pericarditis, containing several distinct, small, spherule-containing granulomas. In two other patients recorded in the same report a diagnosis of pericarditis was made clinically. These two survived the episode and in all three the pericarditis appeared to be the sole manifestation of disease dissemination.

No endocardial lesions were found in the Army Institute of Pathology series reported in 1946 [*4*]. Endocarditis has, however, been described as occurring in this disease in four separate cases. Evans and Ball [*12*] in 1929 reported an instance of "endocarditis due to C. immitis," without further information. In 1936 Abbott and Cutler [*13*] reported an instance with both "adhesive pericarditis and Coccidioidal endocarditis." In 1938 Epstein [*14*] recorded the occurrence of "endocarditis due to C. immitis demonstrated histologically in the valves." The fourth case [*15*] was said to be the youngest patient to have died as a result of coccidioidomycosis, confirmed at autopsy. This revealed the presence of small, reddish nodules on the mitral valve and small yellowish-white nodules on the tricuspid valve leaflets. "These nodules appeared to be a granulomatous inflammatory reaction, rather than the acute destructive reaction of bacterial endocarditis." Sections showed only a chronic scarifying inflammatory reaction. Although no organisms could be found within the valve leaflets, it was presumed that the valvulitis was caused by C. immitis. The patient was three

TABLE IV

EXTRAPULMONARY GRANULOMAS OF C. IMMITIS

Case	Mediastinal Lymph Nodes	Liver	Spleen	Kidney	Skin	Meninges	Adrenal	Thyroid	Bone	Heart	Pancreas	Peritoneum	Prostate	Testis	No. of Organs Involved
1	X	X	X	X	X	..	X	X	..	X	X	..	X	X	11
2	X	X	X	X	X	X	X	X	X	..	..	..	..	..	9
3	X	X	X	X	..	..	X	X	X	X	..	..	..	..	8
4	X	X	X	X	..	..	X	X	X	..	X	..	..	..	8
5	X	X	X	X	X	X	X	X	..	..	..	..	..	..	8
6	X	X	X	X	X	X	X	X	..	..	..	..	..	..	8
7	X	X	X	X	X	..	..	..	X	X	..	..	..	..	7
8	X	X	X	..	X	..	..	..	..	..	X	X	..	..	6
9	X	X	X	..	X	..	..	..	X	..	..	..	..	..	5
10	X	X	X	X	..	..	..	..	..	..	..	..	..	..	4
11	X	X	..	X	..	X	..	..	..	..	..	..	..	..	4
12	X	X	..	..	..	X	..	..	..	..	X	..	..	..	4
13	X	..	X	..	..	X	..	..	..	..	..	..	..	..	3
14	X	..	..	..	..	X	..	..	..	..	..	..	..	..	2
15	..	..	X	..	..	X	..	..	..	..	..	..	..	..	2
16	X	X	..	..	X	..	..	..	..	..	..	X	..	..	4
17	X	..	..	..	..	..	..	..	..	X	..	..	..	..	2
18	X	X	X	..	..	..	..	..	..	..	..	..	..	..	3
19	..	..	..	..	..	..	X	..	..	..	..	..	..	..	1
20	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0
21	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0
22	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0
Total cases	17	14	13	9	8	8	7	6	5	4	4	2	1	1	..

weeks old on admission to the hospital; her death was due to coccidioidal meningitis.

Cases of the Present Series. The microscopic histopathology of the heart in coccidioidomycosis is illustrated and described in Figures 2, 3 and 4. Table IV summarizes the organ or system distribution of anatomic lesions containing spherules of C. immitis. It has been clearly demonstrated that the heart was involved by the spherules of C. immitis in only four patients whereas fourteen patients showed the presence of a variety of cardiac inflammatory lesions at autopsy. Three of the four patients with cardiac granulomas of C. immitis had dissemination to not less than seven distinct and separate anatomic structures. Except for the one instance (Case 16) wherein direct extension of the disease from the mediastinal lymph nodes or pleura to the heart occurred, the frequency of cardiac granulomas of C. immitis was proportional to the degree of dissemination.

In Cases 20, 21 and 22 autopsy disclosed localized, encapsulated pulmonary coccidiomas. In none of these three cases were there specific spherule-containing inflammatory cardiac lesions. In two of these cases, the patients showed myocardial infarcts secondary to arteriosclerotic disease (Cases 21, 22) and one (Case 20) exhibited a mild, non-specific lymphocyte–rich epicarditis and both perivascular and left ventricular subendocardial fibrosis. One patient, Case 19, demonstrated the occurrence of smoldering C. immitis granulomas in the adrenal gland only. Mediastinal coccidioidomycotic lymphadenitis was present without any evidence of pulmonary disease in Case 12; in this instance there was spread of the disease to the liver, pancreas and leptomeninges. There were two cases of coccidioidomycosis spread by direct extension without vascular dissemination to distant organs. The first has already been mentioned (Case 16), in which the heart was the only extrapulmonary site of disease. The second was in Case 15, in which the pulmonary process extended upward into the neck with formation of cutaneous fistulas, and inferiorly through the diaphragm to involve the liver and peritoneum.

SUMMARY

Clinical and pathologic evidence of cardiac involvement was found in six of twenty-two autopsied patients with coccidioidomycosis. Dyspnea and/or orthopnea was present in each of these six patients but was absent in all others, including those with equally severe pulmonary involvement.

Coccidioidal pericarditis, with pericardial effusion at some time during the course of the

disease, was present in three of the six patients. The pericarditis was symptomatic in all cases. Clinical evidence of pericarditis included chest pain, an enlarged cardiac silhouette, a weak cardiac pulsation at the time of fluoroscopy, S-T segment elevation, low and inverted T waves, ankle edema and cyanosis.

A severe myocarditis was present in each of the six patients and may have been important in producing some of the symptoms. Coccidioidal spherules were found in the heart in four of these six patients. In the other two patients chronic non-specific inflammatory lesions were present in all layers of the heart. There was a correlation between the duration of cardiac symptoms and the "age" of microscopic cardiac lesions.

Eight other patients without clinical evidence of heart disease also had chronic, non-specific inflammatory lesions in the heart. These lesions, however, were smaller in size and fewer in number.

No instance of endocardial involvement by coccidioidal spherules was encountered. However, non-specific inflammatory and scarifying reactions were present in the mural endocardium.

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Hydatid Disease in Alaska*

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HYDATID disease (echinococcosis) occurs wherever there is a close association between man and the canine family in the presence of Taenia echinococcus and a suitable natural intermediate host. Infection in man results from contamination of the hands or food and drinking water by the feces of infected canines. Dogs, foxes and wolves act as the final host with a variety of ruminants, pigs and small rodents serving as intermediate larval hosts. In Alaska the requirement of close association between man and dog is fulfilled to an inordinate degree. This is especially so among the native population, the diet of the ubiquitous sled dog consisting in large part of the raw offal of intermediate hosts.

Two forms of Echinococcus species have been recognized in the Alaskan area, E. granulosus (Batsch, 1786) and E. sibiricensis (Rausch and Schiller, 1954) [*1*] which is a form of E. alveolaris (Klemm, 1883) [*2*]. Investigations indicate that E. granulosus is widely distributed throughout continental Alaska [*1,3,4,5*]. E. alveolaris so far has been found on St. Lawrence Island [*1*], and the Komandorskii Islands [*6,7*] and more recently on the Alaskan Coast and Brooks Range [*8*]. The two forms have differences as to intermediate hosts and this fact is of epidemiologic importance. E. granulosus occurs in wolves in the adult form, with moose and possibly caribou and other deer as the intermediate larval hosts [*4*]. Dogs become infected by the adult tapeworm when they consume the viscera of ruminants infected by the larval stage. The adult of E. alveolaris occurs naturally in the arctic and red foxes with various species of small rodents acting as intermediate larval hosts. Dogs become infected when they consume rodents harboring the larval cestode [*4*].

Man is an accidental intermediate host, being readily infected by both forms of Echinococcus found in Alaska. Reports from other parts of the world, where investigation has been in evidence for a longer period, point to the importance of echinococcosis as a human disease [*9–16*].

The Parasite. There is considerable confusion as to the proper nomenclature of the Echinococcus species in general, and for E. granulosus, the causative agent for cystic hydatid disease, the literature goes back to 1786. It is generally conceded that Virchow in 1855 was the first to recognize the multilocular type of cystic development which Klemm [*2*] called E. alveolaris in 1883. Thomas [*18*] considers that E. sibiricensis and E. alveolaris should be synonymized. Other possible synonyms may be obtained from Meggitt [*19*]. Rausch himself states that E. sibiricensis may prove to be identical with the Eurasian type of E. alveolaris. However, there are insufficient data available at this time to support fully the contention that these two organisms are either one and the same or are different. For the purposes of this report the nomenclature E. alveolaris will be used.

The Echinococcus situation on Bering Island in the Komandorskii group as described by Barabash [*6*] and Afanas'yev [*7*] appears to be epizootiologically identical with that on St. Lawrence Island. On Bering Island Clethrionomys rutilus is the intermediate host and this same species is also an important intermediate host on St. Lawrence Island [*3*].

Table 1 summarizes the known differences between E. granulosus and E. alveolaris. Differences in the larval stage occur abundantly, both morphologically and developmentally. The larval stage may be differentiated by the fact that E. granulosus larva develops as a large single cyst characterized by slower growth and a well defined host connective tissue response resulting in a capsule. According to Rausch, such response does not occur in the faster developing multilocular cysts of E. alveolaris. Daughter cysts in E. granulosus are the result of endogenous budding while those of E. alveolaris occur by rapid exogenous budding producing

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what Rausch describes as a rapid malignant growth in the liver of voles. On the other hand, Mankau [*26*], who successfully infected 70 per cent of white mice, stated that the primary larval vesicle undergoes both exogenous and endogenous budding. Although all members of the canine family may harbor the adult cestode of both forms, the literature does not cite the demonstration of E. granulosus in the fox or E. alveolaris in the wolf. Both forms, however, are found in the dog.

TABLE 1
DIFFERENCES BETWEEN ECHINOCOCCUS GRANULOSIS AND E. ALVEOLARIS

Data	Larva	
	E. Granulosis	E. Alveolaris
Vesicle development	Fourteen days [*21*]	Three days [*24*]
Larval follicle at twenty-one days	250–350 mm. [*21*]	Three mm. [*24*]
Connective tissue reaction	Present [*21*]	Not present [*24*]
Secondary vesicles	Endogenous [*22*]	Exogenous [*24*]
Adult hosts	Dog [*23*], wolf [*4*]	Fox, dog [*4*]
Larval hosts	Cattle, sheep, pig, moose, caribou [*4*]	Clethrionomys rutilus, Citelus undulatus, Sorex jacksoni, Microtus oeconomus [*3,19*]
Cystic growth	Relatively slow [*9*]	Relatively rapid [*24*]
Distribution	Iceland, Europe, Africa, South America, Australia, New Zealand, Uruguay, Argentina, Alaska	Europe, Asia, Bering Sea Islands, Arctic Coast of Alaska.
Site of larval development	In human; 65 per cent liver, 24 per cent lung, remainder in other organs [*14*]; in Alaska moose; always in lungs	Liver, 100 per cent of cases in rodents [*24*]
Adult morphology	Testes extend above genital pore [*26*]	Testes below genital pore [*26*]

The larval forms show a high degree of intermediate host specificity. On the Alaskan mainland, according to Rausch, the intermediate hosts of E. granulosus are moose, caribou and deer. There is no record of natural rodent infection with E. granulosus on the mainland. Observations on a variety of experimental animals (cricetids, murids, sciurids, geomids) to which infective eggs were administered have supported the view that voles are readily infected by E. alveolaris, but no success has been achieved in the infection of rodents with E. granulosus. Further observations indicate that infection by the larval stage in moose (at least in southern Alaska) is regularly situated in the lung and that all rodents so far examined show parasitization by the larva in the liver [*24*]. On the other hand, Mankau has shown that larval development in experimentally infected laboratory white mice could also occur in organs other than the liver such as lung, kidney, spleen, pancreas and alimentary canal [*26*].

Investigations into the viability of Echinococcus species ova show them to have a vitality much greater than could be anticipated. Dévé showed that the eggs of E. granulosus kept in ordinary water at room temperature for sixteen days and also those which had been subjected to desiccation for eleven days were infective to squirrels. He also showed that fecal material containing eggs of E. granulosus which had been refrigerated between −1 and +1°C. for 116 days were infective to the suckling pig [*27,28*]. Thomas has shown that eggs in water at 2°C. are still viable after one year [*29*]. In 1955 Schiller reported that the eggs of E. alveolaris, after exposure to a constant temperature of −26°C., were still viable after 360 days. He also investigated the effects of exposures to −56°C. and ova exposed to −26°C. within the carcasses of arctic foxes. On the basis of the results of these experiments he concluded that, after freezing, the duration of exposure seems to be more deleterious than the extreme of cold to which the eggs are exposed. He noted that a somewhat longer period of exposure is required to destroy the eggs of E. alveolaris within the carcass of the fox than after their removal, indicating that some protection may be afforded by the carcass [*30*].

Environmental Factors. As shown in the previous section the cold resistance of Echinococcus ova is such that the cold arctic and subarctic climate of Alaska may not appreciably affect their viability. The experiments carried out to determine cold resistance were performed in the laboratory under artificial conditions; this raises the question of the applicability of these findings to the situation as it exists in nature. However there are certain factors that occur in nature which would tend to imply that the laboratory investigations were in fact more extreme than those normally encountered under natural conditions. It has been shown that wide variations of ambient air temperature have only a small effect on subnivean temperatures. Johnson [*31,32*] and Pruitt [*33*] have shown that with ambient air temperatures as low as −55°F. there is a sharp increase in temperature gradient

down through the snow cover and that subnivean temperatures can be as high as −1°C. (+30.2°F.) and only occasionally lower than −6°C. (+21.2°F.). Pruitt further showed that subnivean temperatures are relatively free of the wide variations of ambient air temperature. It is therefore reasonable to assume that ova which are snow covered are probably never subject to the temperatures of −56°C. (−69°F.) used by Schiller. As Schiller pointed out, it is likely that Echinococcus ova survive throughout the winter and the epidemiologic implications of this are far reaching. Such laboratory data indicate that there is a need for further investigation of the viability of ova under natural conditions during both summer and winter. Especial attention should perhaps be paid to that critical period between summer and winter, and vice versa, when a series of freezing and thawing periods occur and when thermal turnover [*33*] takes place. This period, herein called the thermal turnover occurs when the winter deep ground temperatures, which are relatively warmer than surface temperatures, change over to the summer condition when the reverse is true.

Definitive Host Factors. As can be seen from Figure 1, the fox is the ascertained definitive natural host of E. alveolaris, the wolf is the ascertained natural definitive host of E. granulosus in Alaska. The domestic dog appears to be as easily infected with the adult cestode of both forms and it is reasonable to assume that man is, in the majority of instances, infected directly or indirectly via the dog. However, the possibility of infection among trappers and handlers of raw fur with E. granulosus via the wolf and with E. alveolaris via the fox by the same means cannot be ruled out.

The maintenance of a large dog population for transportation purposes is, and will be for some time to come, an integral part of the Alaskan way of life. For the most part of the year these dogs are nourished by feeding with dried fish interspersed with the raw offal of moose, caribou and other animals that may be available. The dogs are generally tied close at hand in the villages and puppies are allowed to run free. During the course of a week, dogs are frequently handled during feeding, harnessing, and the like. Children constantly play with the dogs.

Table II summarizes the data on the rate of infection in the definitive hosts in Alaska. Rausch has found that as many as 25 per cent of the dogs in some of the Arctic villages may be infected and more than 10 per cent of all Alaskan wolves examined harbored the adult E. granulosus. Of 121 wolves he examined from the Anaktuvuk Pass region, 25 per cent were infected [*4*].

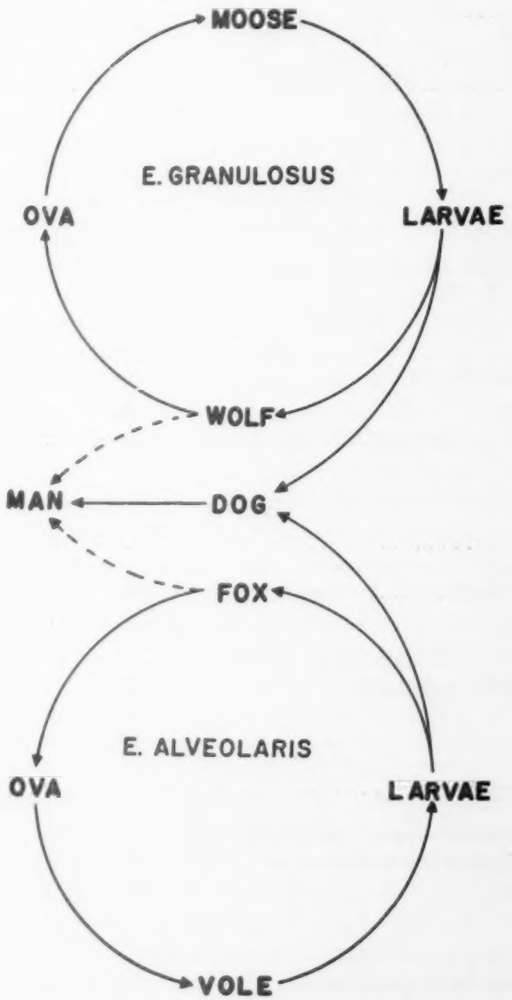

FIG. 1. Life cycles of Echinococcus species in Alaska.

Although the sampling of foxes (when these are given in the literature) is small, the indication that there is a high rate of infection with E. alveolaris is irrefutable. It is believed that E. alveolaris was brought to St. Lawrence Island by arctic foxes coming in on the pack ice from Siberia [*41*] but unfortunately there is little information available on the occurrence of E. alveolaris larva in Siberia.

The Intermediate Hosts. Table III summarizes the knowledge to date on the rate of infection in intermediate hosts. Rausch states that in the

TABLE II

DATA ON RATE OF INFECTION IN DEFINITIVE HOSTS

Definitive Host	Animals Examined (No.)	Infected with E. Granulosus (%)	Infected with E. Alveolaris (%)	Information Source	Locality
Wolf	...	10	....	Rausch [4]	All wolves in Alaska
Wolf	121	25	....	Rausch [4]	Anaktuvuk Pass
Dog	...	25	....	Rausch [4]	.....
Fox	...	..	75	Rausch [35]	St. Lawrence Island
			95	Rausch [35]	St. Lawrence Island
			65	Rausch [35]	St. Lawrence Island
			65	Rausch [35]	Nunivak Island
			5.8	Rausch [35]	Icy Cape
			66	Thomas [19]	St. Lawrence Island
			85	Thomas [19]	St. Lawrence Island

TABLE III

DATA ON THE RATE OF INFECTION IN INTERMEDIATE HOSTS

Intermediate Host	Hosts Examined (No.)	Infected with E. Granulosus (%)	Infected with E. Alveolaris (%)	Information Source	Locality
Moose	...	50 (estimate)	....	Rausch [4]	Matanuska Valley
Caribou	200	0.5	....	Rausch	.....
	253	.....	....	Dunagan [35]	Taylor Highway
Citellus undulatus	12	.....	16.6	Thomas [19]	St. Lawrence Island
	30	.....	0.0	Rausch [8]	St. Lawrence Island
	44	.....	0.0	Thomas [30]	St. Lawrence Island
Sorex jacksoni	4	.....	25	Thomas [19]	St. Lawrence Island
	13	.....	26	Rausch [8]	St. Lawrence Island
Microtus oeconomus	198	.....	17	Thomas [19]	St. Lawrence Island
	200	.....	15.5	Rausch [8]	St. Lawrence Island
	74	.....	13.5	Thomas [19]	St. Lawrence Island
	...	.....	16.0	Thomas [19]	St. Lawrence Island
Clethrionomys albiventer	6	.....	33.3	Rausch [8]	St. Lawrence Island
	...	.....	50	Barabash-Nikiforov [6]	Commander Islands

vicinity of Palmer, in the heavily cultivated Matanuska Valley, almost every aged moose is infected, and he estimates that the larvae of E. granulosus may be found in at least 50 per cent of adult animals. These were found in the lungs, none were found in the liver. He further states that wolves are rare or absent in the Palmer area and other species must serve as the final host. He points out that, in view of their method of feeding, it is surprising that moose have much opportunity to ingest eggs; on the other hand, because of the feeding habits of caribou it would seem that they would be more easily infected. Of more than 200 caribou examined by Rausch only one was found to be infected [4]. Of 253 livers and forty samples of lungs of caribou from the Taylor Highway area examined by this laboratory, no infection with hydatid disease was found [35]. The close relationship known to exist between the wolf and the caribou makes the

finding of both Rausch and this laboratory difficult of interpretation. This situation may possibly be explained by the differences in movement habits of the moose and caribou. Moose as a general rule stay in one locality during their lifetime, continually covering the same feeding ground, and are also strongly aquatic in their feeding habits. On the other hand caribou migrate and are continually on the move, seldom covering the same ground over a considerable period of time. They do not feed in marshes or ponds. Furthermore, wolves follow the caribou herd and seldom precede it.

With regard to E. alveolaris, the significant rates of infection found in Sorex jacksoni (shrew), Microtus oeconomus (tundra vole) and Clethrionomys albiventer (red-back vole), even with small sampling numbers in some cases, adequately show the importance of these rodents as intermediate hosts of E. alveolaris; but there is a wide gap in our knowledge of the relative proportions of these rodents. It is known that M. oeconomus has the greatest population on St. Lawrence Island. On the other hand, it is not known what effect E. alveolaris infection has on their life span and life table.

Man as an Intermediate Host. In the life cycle of Echinococcus species man acts as a dead-end intermediate host, and, as with other intermediate hosts, man becomes infected by ingestion of the ova. How well he participates in this role is still a subject for investigation and determines the effect of the parasite on his well-being.

The cysts of E. granulosus have been found in practically every organ of the body in humans [*11*]. The liver is the most common site for these cysts, being the primary location in 65 per cent of patients; of these the right lobe is involved in 85 per cent. The lung is the next most frequent site of location, occurring in 24 per cent of the cases [*13*]. E. granulosus cysts of the liver may continue to grow for many years or throughout a person's life without producing any signs except enlargement to the liver and some accompanying vague subjective complaints such as a sensation of fullness or of weight in the epigastrium [*14*]; or the cysts may produce disturbing and vague symptoms which can produce physical and mental deterioration, as in the case reported by Zelman [*9*]. In this case it was believed that the infection had been contracted by the veteran patient in Africa in 1943 but symptoms did not start until 1954. In 1947 Weinberg [*10*] performed an autopsy on a veteran of the first world war who died of alveolar hydatid disease in New York and it was concluded that he had been infected in France in 1918.

For a number of years, E. granulosus cysts in the lungs have been noted in x-ray plates taken in tuberculosis surveys in Alaska. At Fort Yukon alone, five persons in whom lung cysts were observed have been successfully treated by surgical methods which confirmed the diagnosis of hydatid cystic disease of the lung [*5*]. Rausch [*8*] states that on the Alaskan mainland in the last three years about fifteen cases have been diagnosed following the finding of the tuberculoma-like bodies in routine x-ray examinations for tuberculosis and the diagnoses have been confirmed by surgical removal of the larval cestode.

Table IV summarizes the rates of hydatid disease in Alaska as determined by complement fixation and skin tests. Persons and Rausch tested 112 natives by complement fixation in Beaver, Tanana and Stevens Village and 20 per cent of these reacted positively [*36*]. Tulloch, of this laboratory, using a Lilly antigen prepared from Taenia pisiformis skin-tested 168 persons from Fort Yukon, Beaver and Tanana and found 21.4 per cent of positives [*5*]. This agrees with the complement fixation findings of Persons and Rausch for the same area. Because the preparation Tulloch used was not accompanied by a control fluid, certain difficulties of reaction interpretation were encountered. To date Rausch has found that complement fixation performed on serums from Gambell on St. Lawrence Island resulted in 7.8 per cent of positive reactors among military personnel and 15 per cent of positive reactors among the native population [*8*]. In 1951 Hitchcock skin-tested 366 persons in Kotzebue with a Lederle antigen made from Dypilidium caninum and reported 3.2 per cent of positive reactors [*37*]. This year this laboratory, using a Casoni fluid from the Biological Laboratories in New Zealand, skin-tested 104 people at Fort Yukon and found sixteen per cent of positive reactors.

Diagnosis in man is at best difficult. In Zelman's case the presence of hydatid disease was not suspected until aspiration produced a hypersensitivity reaction and the characteristics of the aspiration fluid had been determined. Prior to this the symptoms, together with negative x-ray findings, had resulted in a diagnosis of chronic paranoid schizophrenia [*9*]. In Weinberg's report of the autopsy case cited, he stated that the presence of our troops in Europe

TABLE IV
HUMAN ECHINOCOCCOSIS RATE IN ALASKA

Subjects Tested (No.)	Test Used	Positive E. Granulosis (%)	Positive E. Alveolaris (%)	Information Source	Locality
112	Complement fixation	20	....	Persons and Rausch [*36*]	Beaver, Tanana, Stevens Village
168	Skin test (Lilly)	21.4	....	Tulloch [*5*]	Fort Yukon, Tanana, Beaver, Stevens Village
153	Complement fixation	....	7.8	Rausch [*8*]	St. Lawrence Island, Gambell, (Military Personnel)
283	Complement fixation	....	15	Rausch [*8*]	Gambell, St. Lawrence Island (Eskimo)
366	Skin test (Lederle)	3.2	....	Hitchcock [*37*]	Kotzebue
104	Skin test (Biological Laboratories)	16	....	Davis	Fort Yukon

during World War II must force us to entertain the prognostic suspicion that similar cases will be encountered in the inhabitants of the United States in the future [*10*]. A similar statement may be applicable to military personnel in Alaska.

Both forms of the disease can be treated only by surgery. Treatment of cystic disease of E. granulosus is relatively simple and successful. With regard to E. alveolaris, Semenov [*15*] observed sixty-two cases over a period of ten years. Forty-two of these proved inoperable and only two-thirds of the remaining twenty cases were treated successfully.

Transmission. Probably the most dangerous threat to man is from infected dogs, although infection by foxes and wolves may occur. These remarks imply infection by direct contact but there is mounting evidence that infection may occur via water, food and by fly transmission [*38,39,40*]. The viability of ova in water and their resistance to cold and desiccation suggest that water and inhaled dust may be routes of transmission to man. These laboratory findings pose new epidemiologic problems in the field and their importance is still to be determined.

Transmission by flies is a strong possibility. In 1929 Ross [*16*] stated that since flies are known to ingest Echinococcus eggs, and may carry these from dog feces to food, every effort should be made to trap flies and limit their numbers. Other workers have shown the possible importance of flies in the dispersal of ova of parasitic worms [*38,39*]. In 1954 Schiller reported an experimental study on blowfly (Phormia regina) transmission of hydatid disease. Using voles he found that three of eight voles became infected by fly transmission. Schiller further pointed out that very little information is available on the occurrence and distribution of members of Calliphoridae in Alaska. The feeding habits and type of life cycle of Calliphoridae appear to favor opportunities for acquisition and dispersal of Echinococcus eggs. Blowflies feed and breed readily on the excrement of canine animals and are also attracted to fresh meats and human foodstuffs. These relationships may be significant on the Arctic slope and on St. Lawrence Island where the natives subsist mainly on a diet of meat which is often eaten raw and unwashed [*40*].

COMMENTS

The Alaskan situation with regard to Echinococcus clearly indicates that research effort in this area has been fragmentary, Rausch being the only consistent worker in this field. There are too many gaps and unknowns yet to be resolved. The results so far show that two types of Echinococcus occur in Alaska—E. granulosus and E. alveolaris. These two species have life cycles which are so different as to create two specific problems from the epidemiologic, and eventually from the control, points of view. The results of skin tests and complement fixation tests indicate that the problem may be widespread not only in Alaskan natives but also in military personnel stationed in Alaska. The military implications of this are far-reaching and deserve special attention. As yet, data have been obtained only from military personnel stationed at Gambell on

St. Lawrence Island, and the rate in these personnel, as determined by complement fixation is about half the rate found in the natives of Gambell for E. alveolaris. If reliance can be placed on the complement fixation reaction used, this rate is alarming and clinical cases can be expected in the future. Seminov's findings regarding the poor results of treatment of E. alveolaris places a high priority on methods of control and prevention. No examination of troops in other areas of Alaska is available in the literature but a program by this laboratory is already planned to achieve this.

The full extent of the rate of infection both in the natural intermediate hosts and in the natural definitive hosts, and the effect of this infection on their respective life tables, is relatively unknown. Only six studies of the rate of infestation in the human population are recorded in Alaska and they give only an incomplete picture of the possible extent of the problem. The food habits and living conditions of native Alaskans greatly facilitate the possibility of their acquiring both forms of echinococcosis. Investigation of one group of military personnel shows that they are not immune to parasitization and this suggests routes of transmission other than direct contact with canines harboring the adult cestode. The longevity of the larval state in man and the possibility of serious and ill-defined end results of parasitization makes definition of the extent of the problem by surveys of paramount importance both to military and civilian populations.

SUMMARY

The results of a study of echinococcosis in Alaska indicate that the disease is widespread both on the Alaskan mainland and the Bearing Sea Islands. Two etiologic agents have been demonstrated. These have widely separated epizootiologic and epidemiologic characteristics.

On the basis of the data presented it is concluded that much field and laboratory investigation is still necessary before a proper understanding of the significance of the disease and its control can be achieved.

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Review

Temporal Lobe Epilepsy: Brief Review*

Responses on Electrical Stimulation of the Amygdaloid Region in Six Patients

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DURING the past two years electrical coagulation of the amygdaloid region has been used as a therapeutic procedure in six patients with temporal lobe seizures. Prior to coagulation the implanted electrodes were used for studying the effects of electrical stimulation of the amygdaloid region and for recording the electrical activity from this region. The purpose of this paper is to review briefly the subject of temporal lobe epilepsy and to summarize the findings in our own cases.

Of the epilepsies, temporal lobe epilepsy, despite its high frequency, is perhaps the least appreciated variety. It deserves wider appreciation in view of its incidence and its relative intractability to medical therapy and its great social and economic importance. Clinico-anatomic correlations, studies of the temporal lobe by electrical stimulation, and the recording of the electrical activity of the brain in patients with this disease are contributing richly to our meager knowledge regarding temporal lobe epilepsy and the physiology of the temporal lobes.

Temporal lobe epilepsy comprises a group of manifestations having in common a site of discharge in the region of the temporal lobe. It is, therefore, a form of focal epilepsy. The clinical pattern of these seizures probably varies with the precise situation, direction and extent of the spread of discharge; and the varying clinical picture has led to the use of a number of terms such as psychomotor epilepsy, uncinate epilepsy, psychic epilepsy, and epilepsy with an intellectual aura. Each of these terms describes some aspect of the seizure; none suffices to describe the group as a whole. Temporal lobe epilepsy is probably the more inclusive and better term than any of these.

The first descriptions of what is now called temporal lobe epilepsy appeared in 1888 in an article by Jackson [*3*] entitled, "On a Particular Variety of Epilepsy." In this paper, based upon the notes of his fifty cases, he described in detail the clinical features of the disease which until then were not recognized as being epileptic in nature. In his description of these seizures Jackson paid particular attention to what he called the dreamy state, a state in which there is a vague recollection of something long forgotten, abrupt, transient and recognized by the patient as abnormal. The symptoms observed by Jackson to be frequently associated with the dreamy state were: crude sensations of smell and taste; elaborate hallucinations of sight or, occasionally, of hearing; an epigastric sensation; a feeling of dread; movements of the lips and jaws resembling those of chewing, tasting or spitting; aimless movements of the limbs, coordinated, not convulsive, and finally, "exceedingly complex and very purposive-seeming actions during continuing unconsciousness."

Later papers by Jackson [*4*] established that this variety of epilepsy could be associated with

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organic disease in one or the other temporosphenoidal lobes. Jackson's best documented example was the case of a physician who had major and minor seizures from age twenty until his death at the age of forty-three. In one of his attacks, he made a difficult crossing of a Swiss glacier. During another seizure, he examined a patient, made the correct diagnosis and prescribed adequate treatment. He died at the age of forty-three from an overdose of chloral and, at autopsy, a patch of softening in the left uncinate region was the only lesion found.

On the basis of postmortem examinations Jackson [*4*] in 1899 proposed the term "uncinate group of fits" for his particular variety of epilepsy. Recent observations by Penfield indicate that some of the manifestations included by Jackson in the uncinate group are evoked by stimulation of parts of the temporal cortex other than the uncinate gyrus. Jackson therefore was right in carefully qualifying that by the uncinate group of fits he meant that the discharge arose from "cells not of the uncinate group alone but of some cells of different parts of a region of which this gyrus is a part."

Unfortunately, due to the influence of Gower's [*5*] writings the impression prevailed for a long time that olfactory aura was essential for the diagnosis of uncinate fits. Actually it is now established that olfactory aura occurs infrequently in uncinate attacks [*6*].

In 1938 Gibbs, Gibbs and Lennox [*7*] introduced a new term, psychomotor epilepsy, based upon the observation of a newly discovered pattern in the electroencephalogram which was thought to be associated with a particular variety of epileptic seizure. The term psychomotor epilepsy gained in popularity, and it was widely supposed that a new clinical type of epilepsy had been defined and that it could be recognized by the electroencephalogram. In the light of knowledge gained, or perhaps regained, since that time, Lennox [*2*] recently reviewed the concept of psychomotor epilepsy. His account of symptoms is included within what he calls the psychomotor triad comprising, (1) motor phenomena, including abnormal behavior, (2) automatism with amnesia, (3) subjective psychic seizures, including the dreamy state, hallucinations of sight, hearing, smell or taste, and episodes of mild confusion. This triad adds little to what was described by Jackson in 1888. Lennox concluded that in view of evidence obtained from various sources the term psychomotor epilepsy might be supplanted by temporal epilepsy. This leads us back, therefore, towards Jackson's concept of the uncinate group of fits.

The clinical pattern of temporal lobe epilepsy is variable but three main grades of seizures can be recognized: (1) minor seizures, (2) psychomotor seizures, and (3) major convulsive seizures.

The minor seizures last from one or two seconds to a few minutes. There are no convulsions and there is no loss of consciousness. The patient may suddenly and briefly experience any of a variety of auras. These auras are characterized as sensory, psychointellectual, emotional and autonomic.

The sensory auras include an epigastric sensation such as a "turning feeling," a "peculiar feeling" in the stomach. This is the commonest aura [*6*] of temporal lobe epilepsy. Penfield and Rasmussen [*8*] have reproduced this epigastric sensation by electrical stimulation of the insular and Sylvian regions. Sensations of taste and smell are experienced but with as low an incidence as 2 per cent in one series [*6*]. Another set of sensory auras concern hearing and equilibrium. The patient may suddenly experience tinnitus and vertigo. These responses have been reproduced by electrical stimulation of the superior temporal convolution [*8*].

The psychointellectual auras include Jackson's dreamy state with varied manifestations. Visual illusions and hallucinations occur in about 8 per cent of the cases [*6*]. Objects may suddenly seem small and distant (micropsia) or unduly large and near (macropsia) or distorted into bizarre shapes (metamorphopsia). The entire surroundings may assume a uniform bright color (erythropsia, cyanopsia). The patient may complain of repeatedly seeing an object that is no longer in his field of vision (pallilopsia). The incidence of auras involving auditory illusions and hallucinations is about the same as that for visual ones. A sudden feeling of familiarity with the surroundings or the reinactment of a past event (déjà vu phenomena), a sudden feeling of unreality or strangeness about common surroundings (jamais vu phenomena) or a feeling of a bizarre transformation of the body (depersonalization) constitute additional features of psychointellectual aura. Similar experiences and past events have been invoked by electrical stimulation of the amygdala [*9*]. Feelings of fear, depression, euphoria, anger or bewilderment are not uncommon.

Those symptoms are regarded as features of emotional aura. The autonomic auras include flushing, pallor, perspiration, awareness of borborygmi, pupillary dilatation and pounding of the heart.

It is the psychomotor seizure that has attracted major attention during the past decade. Attacks may begin with any of the auras which have been described. These are followed by a period, lasting from a few seconds to several minutes, when the patient indulges in motor activities like smacking of the lips, chewing, sucking or swallowing movements, rubbing of the abdomen, grimacing, fidgeting and other semi-purposive movements of the limbs. The patient then displays what is termed automatism for a period lasting from a few minutes to an hour or more. During this period he engages in activities that are seemingly purposive but inappropriate to the occasion. Thus a patient enjoying a game of cards may suddenly get up and start rearranging the furniture in the room or doing the dishes. He does not respond to questions or commands during this period of automatism. If disturbed, he may become belligerent and assaultive. On regaining his contact with the environment the patient has amnesia for the attack except that some may remember the sensory auras that initiated the attack. Thus the chief features of this psychomotor attack are the motor phenomena, automatism and amnesia.

Major convulsions may occur in the most severe grade of temporal lobe epilepsy. They may be indistinguishable from grand mal seizures due to lesions in other parts of the brain unless the initial aura has been recorded. Some patients may have a psychomotor seizure at one time and a generalized convulsive seizure at another. It is fallacious to think that such patients are suffering from two kinds of epilepsy. The distinction between the two types of attacks is one of the extent of the spread over the cortex.

Over the past ten years it has become increasingly apparent that personality disorders, often of severe degree, may be associated with temporal lobe epilepsy. In fact, it is becoming more and more clear that it is the temporal lobe cases that have given rise to the idea of the epileptic personality and epileptic deterioration. Gibbs et al. [*10*] "noted that nearly 50 per cent of all patients with temporal lobe epilepsy show severe personality disorders during interseizure periods." Liddell [*11*] found that the majority of epileptic patients in mental hospitals show temporal epileptic foci on the electroencephalogram. There is no fixed pattern to the epileptic personality. Assaultive, aggressive, hostile behavior is a common finding and these patients are frequently put into the seclusion wards of mental hospitals because of their assaultiveness. Acutely violent outbursts may follow a seizure or occur unrelated to a seizure. In addition, the patient may suffer from depression, paranoia or schizoid states. Falconer [*12*] noted that the personality disorder often gets worse rather than better as the control of fits is achieved by medication.

MATERIALS AND METHOD

Patient Selection. Our patients for electrocoagulation of the amygdaloid region were selected by the Psychiatric Staff of the Boston Psychopathic Hospital. Four of the patients had been selected and referred from the Monson State Hospital for Epilepsy, Monson, Mass. by Dr. Roger Osterheld, director of that institution. The final decision to perform electrical coagulation of the amygdaloid region was made after each patient had been observed in the wards of the Boston Psychopathic Hospital for an eight to sixteen week period. All the patients had a diagnosis of temporal lobe seizures. Each patient had abnormal electroencephalograms as recorded from the scalp preoperatively. The abnormality in all cases was localizable to the temporal lobe, two patients had, in addition, abnormalities localizable to the frontal lobes. Every patient had temporal lobe spiking.

Despite prolonged and intensive medical therapy, these patients had continued to deteriorate. Surgical therapy was being contemplated in an effort to salvage the patients from life-long institutional care. Selective destruction of the amygdaloid complex by electrocoagulation was undertaken in order to avoid the more extensive procedure of temporal lobectomy. In addition to the seizure, uncontrollable assaultive behavior was a major problem in four of the patients. Studies in animals have shown that bilateral amygdaloid destruction makes them docile whereas amygdaloid stimulation evokes rage-like reactions in them [*16,17*].

The preoperative study of the patient included a number of psychologic tests in addition to the psychiatric, neurologic, and routine laboratory examinations. These results will be reported after an adequate follow up and assessment of the therapeutic effects of the amygdaloid coagulation procedure.

Procedure of Electrode Implantation, Electrical Stimulation, and Electrical Recording. The details of these methods will be reported elsewhere. Skull x-ray visualization of the air-filled tip of the temporal horn and the anterosuperior aspect of the posterior clinoids

were used as guides to implant the four wire electrodes in the amygdaloid region. The implantation was made through a trephine opening, 15 mm. in diameter, in the temporal bone. The electrodes were secured in place by attaching the cable containing the four leads to the bone or by securing the individual lead wires to a teflon washer that was suspended in the trephine opening by wire sutures. The wound was then closed. The electrodes wires emerged from the scalp at the upper end of the wound and were covered by head bandages.

Electrical stimulation could be performed between any two of the depth electrodes by means of a Grass model 3C stimulator. This delivered a monophasic square wave through a stimulus isolation unit. The stimulus was controlled with respect to pulses per second, pulse duration and voltage. The current was monitored oscillographically except for the studies in the first four patients. The impedance of the brain tissue in three patients was measured periodically by an alternating current ohmeter. The duration of each stimulation was varied depending on the response obtained. Any change in skeletal motor or autonomic activity or in feeling states produced by electrical stimulation was regarded as a positive response.

The blood pressure, heart rate and respirations were recorded by means of a Sanborn electromanometer and a 4-channel polyviso with polyvinyl catheter in the femoral artery and with a pneumatic cuff attached around the chest. Subjective responses were elicited by neutral and direct questions and when important, they were documented by a tape recorder. Motor, behavioral and pupillary responses were recorded by a movie camera or still camera. The electrical activity of the brain was recorded by an 8-channel Grass console electroencephalograph. A specially designed lever system permitted central control of the stimulator and the various recording apparatus.

CASE REPORTS

CASE 1. R. B., a sixteen year-old boy, was subjected to electrical coagulation of amygdaloid region in the right hemisphere because of uncontrollable seizures and assaultive behavior. He was born at full term; delivery was uncomplicated and no instruments were used. There was no history of epilepsy in the family. One uncle had "insanity." At the age of six months the patient had meningococcal meningitis and his first convulsion occurred during this illness. He made full recovery but did not become free of convulsions until the age of eighteen months. When he was five years old he fell off an ice truck and remained unconscious for an unknown length of time. At the age of six, he started having seizures again and they persisted thereafter despite intensive treatment with luminal, dilantin and mesantoin. A severe personality disorder developed. The patient frequently exhibited an explosive temper that was difficult to control. Following some of the seizures he became violent and assaultive, struck his mother on one occasion, and cornered his brother with a knife on another. At the age of ten he was committed to the Monson State Hospital for Epilepsy. He averaged forty to fifty seizures a year since his admission. They were of two types. In the minor attacks he suddenly became dazed and confused, and remained so for a few seconds to a couple of minutes. There was no loss of consciousness. Before a major attack he had "a vague feeling in his head that 'something was coming on.'" "It all starts in the stomach"; then there was loss of consciousness and a generalized convulsive seizure. Following some of the seizures he became very defiant, destructive, assaultive and dangerous; he struck other patients, broke window panes with his fist, tore up bed sheets, indiscriminately hurled things all over the ward. He had to be put in seclusion for hours before he quieted down. Such assaultiveness and aggression were also frequently seen without any relationship to an epileptic seizure.

Electroencephalographic findings; preoperative record: The tracings were abnormal with spikes and slow spikes in the right anterior temporal region. An example of the slowing spiking is shown in Figure 1.

Recording from the depth electrodes: There was spiking recorded from the depth electrodes. (Fig. 1.) The spikes might or might not be accompanied by spikes in simultaneous recordings from the scalp over the temporal region. The spikes at the depth electrode increased in frequency during states of drowsiness and became less frequent during states of agitation or increased alertness.

Electrical stimulation findings: This patient was electrically stimulated for a total of seventy times on the fourth, fifth and sixth days after electrode implantation. Positive responses were obtained using 10, 20 or 60 pulses per second, 1 millisecond pulse duration, and 8 to 20 volts. The patient repeatedly remarked during or after electrical stimulation that he got a feeling in his head "as if a spell is coming on." He could not describe this more fully. He also consistently reported experiencing a "weird feeling." When the intensity of the voltage was increased, he looked frightened and drew his arms across his chest as if he were protecting himself from something. These effects were accompanied by alterations in breathing and bilateral pupillary dilatation. Bilateral pupillary dilatation in the absence of subjective or skeletal motor responses could be obtained with as little as five volts. An after-discharge of spikes appeared in the depth electrode recordings frequently in association with the induced clinical responses. Yet the clinical and electrical phenomena produced by electrical stimulation often occurred independently.

The aura of feeling something in his head, "as if a spell were coming on," appeared to be the only aspect of his seizures that was reproduced by electrical stimulation. Epigastric aura and assaultive behavior

was not reproduced by stimulation within the parameters noted above.

CASE II. J. P., a thirty-seven year-old man, was referred to the Boston Psychopathic Hospital for amygdaloid coagulation because of seizures and difficult behavior. He had a history of normal birth, at full term, without the use of instruments. A sister suffered from epilepsy. As a child he had measles and scarlet fever, neither illness being complicated by convulsions. At the age of five years he was kicked in the forehead by a horse. His skull was fractured and he remained unconscious for about three hours. His first seizure occurred at the age of ten, and for many years seizures occurred no oftener than once a year. From the age of twenty-five years onwards the frequency of the seizures began to increase and by the time he was thirty years old he was having weekly seizures which were followed by a period of extreme violence. Following some of the attacks he beat his father, abused and struck his mother and wife, smashed his radio set, and broke up furniture. At the age of thirty, he was committed to the Monson State Hospital. During his seven years in this institution he continued to average four to five seizures a month and continued to exhibit assaultive behavior following the seizures. His seizures showed a varied and complicated pattern. Often, he knew minutes in advance that an attack was coming on. The attack would consist of a period of confusion lasting several minutes to an hour or more. In one of these confusional spells he jumped off a piazza. In another, he made an agitated speech in the dining hall and had no recollection of it later. In still another, he confined himself to his room, appeared to be in a trance, and prayed throughout the duration of the attack. In some of the seizures he looked scared, became disturbed, and experienced auditory and visual hallucinations. In the most severe grade of seizure, following a short period of confusion, he would lose consciousness and have a generalized convulsion. Outbursts of violent and assaultive behavior followed the seizures as a rule. He hit a patient on the head with a broom stick, bit another patient's thumb; he became very noisy, tore other patients' shirts, attacked anybody in sight, destroyed things within reach, and had to be put in seclusion for several hours before he would quiet down. In between seizures he was quite manageable, likeable, and worked well under supervisors. His general physical examination was unremarkable except for a depression of the frontal bone. He showed moderate mental retardation; otherwise the neurologic examination revealed no abnormal findings. The Hinton test on blood and spinal fluid was negative. Examination of blood and urine and the gold sol curve gave normal values. Normal findings were noted on electrocardiogram, chest film, skull x-rays and pneumoencephalogram.

Electroencephalographic findings; preoperative record: The record showed spike activity over both temporal regions, as well as over both frontal regions. (Fig. 2.)

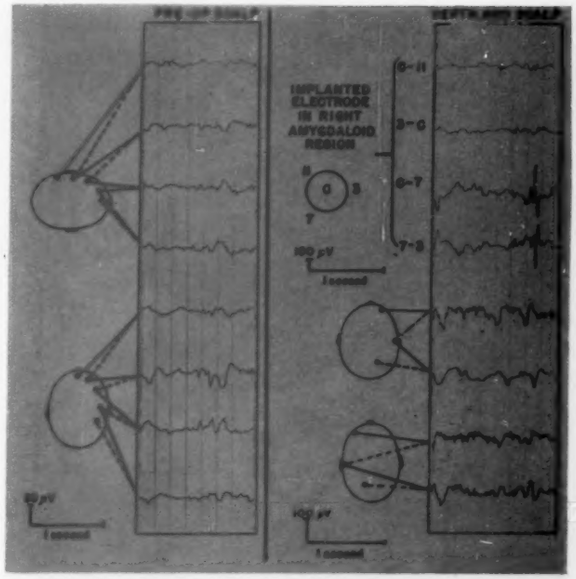

FIG. 1. Preoperative scalp recording and simultaneous depth electrode and scalp tracings recorded after depth electrode implantation. The circle drawn opposite the depth electrode recordings indicates the position of each depth electrode. The locations are to be read as time indicators on a clock face which is positioned over the temporal bone with the patient sitting upright. All the depth electrode tracings shown in Figures 1 through 6 were recorded prior to electrical coagulation of the amygdaloid region. In this figure, the preoperative tracings from patient R. B. (Case I) show slow spikes over the right anterior temporal region. The electrode implanted in the right amygdaloid region shows spiking reversing at lead 7.

Recording from the depth electrodes: Considerable spiking was recorded from the depth electrodes with occasional spikes appearing in the simultaneous recording from the scalp electrode over the temporal region. The spikes in the depth were not always synchronous with those at the scalp but in general they appeared related.

Electrical stimulation findings: This patient was electrically stimulated for a total of twenty-nine times during the third, fourth, fifth and sixth days after implantation of the wire electrodes in the amygdaloid region of the left hemisphere. The positive responses were obtained with 30 to 60 pulses per second, 1 millisecond pulse duration, and 10 to 20 volts. The responses were consistent each time. Initially the patient would stare, look to the right and then to the left, fumble with his shirt, rub his trousers, play with the examiner's fingers, become agitated, try to get up off the bed, raise both his legs and mumble. On several occasions he spoke in

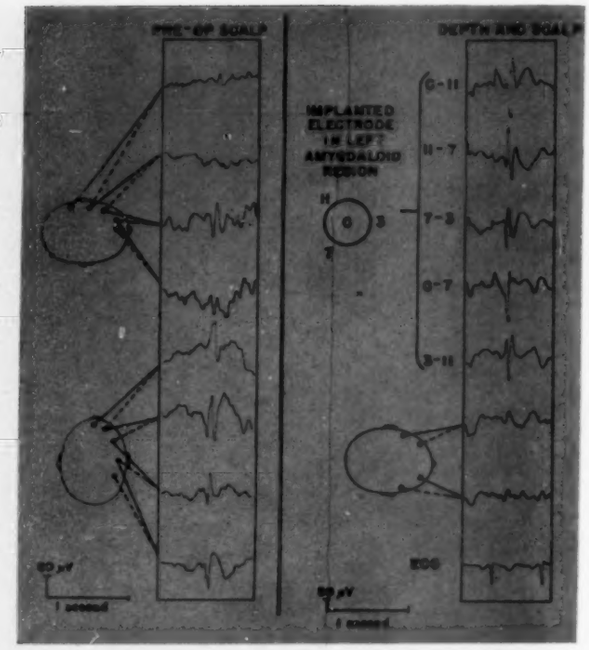

FIG. 2. Preoperative scalp recording and simultaneous depth electrode and scalp tracings recorded after depth electrode implantation. The preoperative tracing from patient J. P. (Case II) shows slow spikes in both frontal regions and also from the right temporal electrode. The electrode implanted in the left amygdaloid region shows spiking in all combination of leads.

Portugese, his native language. During this interval he would become sweaty, pale and cyanotic; he would breathe irregularly; his heart rate would increase from 15 to 40 per cent. After 3 to 5 minutes of such behavior he would become euphoric, smile and mumble a few incoherent remarks. One time he mentioned that "The people were downstairs" and that "one of them was a wolf." Another time he made a religious cross and mentioned the rosary and the church. He would be confused and mostly unresponsive for fifteen to twenty minutes after the end of electrical stimulation. These behavioral changes were associated with an after-discharge in the depth electrode tracing followed by slow rhythmic activity.

It was believed that those aspects of his clinical seizures which were reproduced by electrical stimulation included confusion, automatism and states of agitation. Assaultiveness was not reproduced.

CASE III. I. N., a forty-three year-old pipe fitter, was referred to the Boston Psychopathic Hospital because of increasing frequency of uncontrollable seizures. He had an uncomplicated birth at full term; had measles and mumps during childhood. There was no history of epilepsy in the family. Seizures started at the age of thirty-three years. Occurring initially at monthly intervals, their frequency progressively increased over the next ten years despite intensive treatment with phenobarbital, dilantin and mesantoin. By the time he was forty-three years old he was having seizures at weekly intervals and was therefore unable to carry on at his job. Seizures showed varying grades of severity. In the minor attacks he experienced "strong and funny chemical smells" and the entire attack would consist of this olfactory sensation lasting for five to fifteen minutes. At other times these "peculiar odors" were followed by lapses of two to four minutes during which he would indulge in fumbling movements, look frightened, ramble in his speech, appear confused, and not respond to questions or commands. He would also exhibit bizarre behavior at this time such as walking away from his place of work. Once he had been waiting at his car for his wife who had gone into a drug store. The next thing the patient remembered was that he was driving along the road and was unable to orientate himself. After driving about a mile he became orientated and returned to find his wife waiting in front of the drug store. At the age of forty-one years he showed assaultive behavior for the first time. During a seizure which he had at a subway station he attacked a guard who tried to restrict him and got a jail sentence of three months. Subsequently, he often became assaultive if an attempt was made to restrict him during the spells.

Electroencephalographic findings; preoperative recording: This record was abnormal with spikes in the left anterior temporal region.

Recording from the depth electrodes: Throughout the period during which the electrodes were left implanted, the record showed spontaneous seizure discharges. (Fig. 3.) These increased in frequency and duration from day to day. So far as we could determine, there was no correlation between the many spontaneous electrical seizure discharges recorded from the depth electrodes and the patient's clinical seizures. There was, however, one exception. He was eating his dinner during one period of recording and he suddenly exclaimed, throwing his bread down, "That tastes like sandpaper." The onset of this behavior was simultaneous with the onset of one of his spontaneous electrical seizure discharges. Occasionally the patient would not reply directly to questions but this would occur just as often between as during the occurrence of electrical seizure discharges from the depth electrodes.

Electrical stimulation findings: This patient was electrically stimulated for a total of sixty-two times on the fifth, sixth and seventh day after the electrodes were implanted in the left hemisphere. Positive responses were obtained with 10, 20 or 60 pulses per second, 1 millisecond pulse duration, and 5 to 15 volts. These consisted of the fumbling movements, the facial expression reflecting fear or anxiety, confusion and unresponsiveness that had been noted by the patient's wife on many occasions when the patient was having a spell. Other effects elicited by electrical

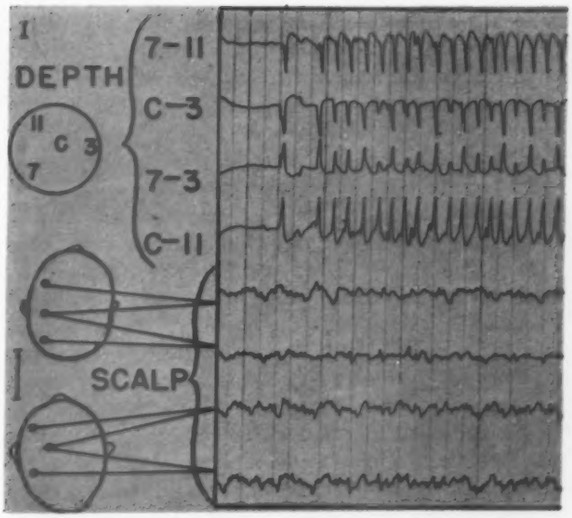

FIG. 3. Preoperative scalp recording and simultaneous depth electrode and scalp tracings recorded after depth electrode implantation. The depth electrode recording from patient I. N. (Case III) shows spontaneous electrical seizure patterns from the amygdaloid region in the left hemisphere. The bandage covering the operative wound prevented scalp electrodes being put over the left temporal region.

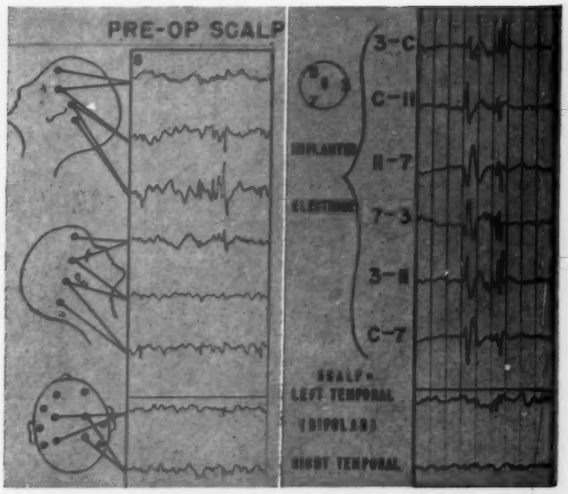

FIG. 4. Scalp and depth electrode tracings. The preoperative scalp recording from patient C. W. (Case IV) shows spike reversing at the mid-temporal electrode on the left and low voltage spikes appearing synchronously in the right frontal region and in the high posterior temporal leads bilaterally. The spikes occur independently of the heart (which can be seen in channel number 6). The depth recording from the electrode implanted in the left amygdaloid region shows high voltage spiking with some simultaneous spike potentials at the left temporal scalp electrodes.

stimulation were "a feeling like my body is getting small." "Whoo, that was something." "A shivering with electricity all over my body." One stimulation caused the patient to be unconscious for about five minutes, after which he was disoriented for forty-five minutes. Other responses included excessive sweating, looking to the right and left, altered breathing, interruption of counting or talking, quivering talk, cyanosis, 100 per cent increase in heart rate and a 50 mm. Hg rise in systolic and diastolic blood pressure. The induced clinical responses were accompanied by an after-discharge in the depth electrodes and then extinction of activity and slow recovery.

CASE IV. C. W., a twenty-eight year-old woman, was referred to the Boston Psychopathic Hospital because of assaultiveness and increasing frequency of seizures. History of birth and development was normal. One sister was regarded as psychotic and had seizures. The patient had her first seizure at the age of fifteen years. She began to have periods of screaming, violent and destructive behavior and sulkiness, and at the age of eighteen she had to be committed to the Monson State Hospital. During the ten years at this institution she continued to have frequent seizures, two to eight per month, despite adequate medication with luminal, dilantin and mesantoin. Some of the seizures consisted of just being dazed for a few seconds to a minute or two. On one occasion she appeared confused and dazedly walked out of a church service, a few minutes later she returned again. Several minutes later she fell to the floor and had a seizure with a twitching of her right hand. The major seizures started with a "dizzy feeling," "a strange feeling in the head." This was followed by generalized convulsions in all parts of the body lasting five to ten minutes. Throughout her stay at Monson State Hospital she had frequent periods of assaultive and destructive behavior when she broke window panes, abused and struck other patients, kicked and scratched the nurses and tore their uniforms. She quieted down after being put in seclusion for a couple of days. At times she appeared very disturbed and barricaded herself in a room. No relationship between assaultiveness and seizures was noted.

Normal findings were noted on physical and neurologic examination. Laboratory tests including examination of blood and urine, blood and spinal fluid serologic tests, x-rays of chest and skull, and electrocardiogram were normal.

Electroencephalographic findings: preoperative record: Spiking was noted over the temporal regions as described in the legend of Figure 4. The records were abnormal with slow waves, especially in the frontal leads, worse on the right than on the left.

Recordings from indwelling electrodes in the amygdaloid region of the left hemisphere: There was spontaneous spiking. Sometimes this was synchronous with spike activity recorded from the scalp over the temporal region and sometimes it was not. (Fig. 4.)

Electrical stimulation findings: This patient was

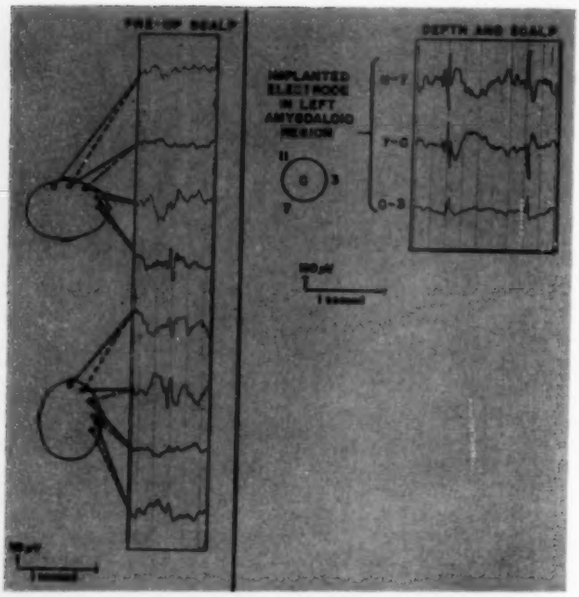

FIG. 5. Scalp and depth electrode tracings. The preoperative tracing from patient W. C. (Case v) shows bilateral spiking from the frontal regions. From the amygdaloid region spike activity such as shown in the figure was recorded on each of the seven days during which the electrodes were in place.

electrically stimulated for a total of thirty-seven times on the third and fourth day after implantation of the electrodes in the left amygdaloid region. The positive responses were obtained with 30, 45 and 60 pulses per second, 1 and 2 milliseconds pulse duration and 10 to 24 volts. The responses included shouting out, looking with alarm to the right or left or both ways, confusion, unresponsiveness, and apparent recall of events. During and after one stimulation she shouted, "There he goes now." When asked what she meant, she replied, "He tried to hug me up." "The police will get him." She looked scared. Other responses to electrical stimulation consisted of changes in breathing, bilateral pupillary dilatation, and a 30 to 70 per cent increase in heart rate. No after-discharge occurred from the depth electrodes without an associated clinical response. Yet a clinical response could be elicited in the absence of such an after discharge. No assaultiveness was reproduced.

CASE V. W. C., a thirty-six-year-old man, was referred to the Boston Psychopathic Hospital because of assaultiveness and seizures. Birth and development history was normal. One brother was regarded as mentally defective; he never attended school and never left home. The patient had his first seizure at the age of twenty-three years and he continued to have seizures at the rate of one to two a month. At the age of twenty-six years, after a seizure, he became extremely assaultive, struck his father and mother and became so violent that the police had to be called. He had complete amnesia for this event. After a couple of such assaultive episodes following seizures he was committed to the Monson State Hospital at the age of twenty-six. During his ten years' stay at this institution he became progressively worse, with increasing frequency of seizures, three to eight per month. Seizures consisted of generalized convulsions lasting about ten minutes. Swallowing movements were observed before many of these convulsive seizures and some of them were followed by aggressive, assaultive and destructive behavior. More often, he had episodes of assaultiveness without convulsions. For hours he would be confused and dangerous. During these confusional spells he struck fellow patients with chairs, broke several patients' noses, and once cornered an attendent in the kitchen with a knife. No improvement occurred despite intensive therapy with phenobarbitol and dilantin.

Physical and neurologic examination revealed normal findings. Laboratory tests including routine blood and urine analyses, blood and spinal fluid serologic tests, and x-rays of chest and skull were normal.

Electroencephalographic findings; preoperative record: After overbreathing, rare spiking was noted over both temporal regions, more marked on the left than on the right. An example of frontal spikes is seen in Figure 5. The record also showed slow activity, more marked in the frontal regions near the midline.

Recording from the depth electrodes: Spiking was present from the depth electrodes at the time of implantation when the patient was under moderate pentothal and nitrous oxide anesthesia. Spontaneous spiking from the depth electrodes of the type seen in Figure 5, continued over the next seven days.

Electrical stimulation findings: This patient was stimulated for a total of ninety-six times on the fourth, fifth and eighth day after the electrodes were implanted in the left hemisphere. The positive responses were produced with 60 pulses per second, 1 millisecond pulse duration, and 10 to 20 volts. Electrical stimulation produced sensations in the head described as follows: "I feel it now." "It is amazing." He could explain nothing more about his feelings. Nor were these sensations accompanied by any changes in skeletal motor behavior. Several times his right hand or one or two fingers of the right hand would slowly contract, and at times contract and relax, during electrical stimulation. So far as we could determine, no aspect of the patient's seizures was reproduced by electrical stimulation. The subjective responses mentioned above were frequently but not always associated with runs of high voltage spike activity from the depth electrodes.

CASE VI. M. C., a twenty-seven-year-old woman, was referred to the Boston Psychopathic Hospital because of intractable seizures. Delivery was difficult and forceps were used, but no apparent birth injury

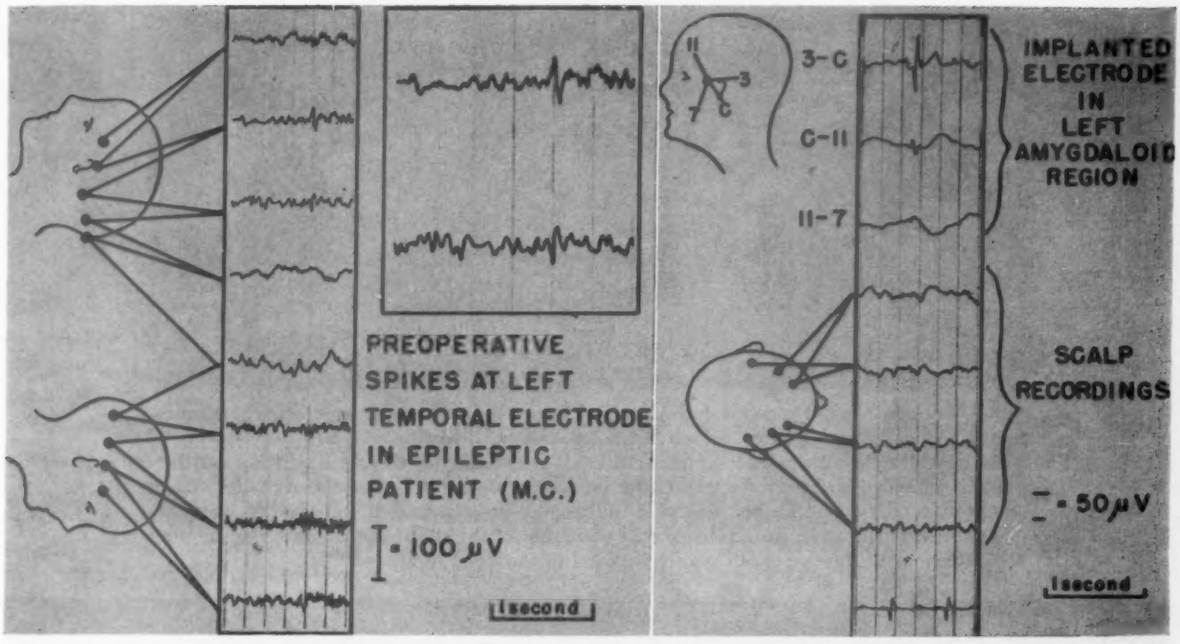

FIG. 6. Scalp and depth electrode tracings. The preoperative record shows spontaneous spiking from the left temporal region in patient M. C. (Case VI). (Insert shows enlargement of channels 2 and 3.) After implantation in the left amygdaloid region spike activity was found in the depth electrode. The simultaneous scalp recording was made from electrodes placed above the temporal region to avoid the operative wound and overlying bandage.

was observed. Convulsive seizures began at the age of one year and infrequent seizures—intervals unknown—continued throughout childhood and adolescence. At age fifteen she left school because of "epilepsy." From fifteen onwards she had generalized seizures, averaging one a year. At the age of twenty-six a new and different kind of seizure developed characterized by sucking of thumb, clenching of fist, jerky movement of arms, grimacing, confusion, unresponsiveness and amnesia. Despite intensive medications with luminal, dilantin and mesantoin, seizures increased in frequency to two to eight a month.

Physical and neurologic examinations revealed no abnormalities. Laboratory tests including routine blood and urine analyses, X-rays of the chest and skull, and electrocardiogram were normal.

Electroencephalographic findings; preoperative record: Spike activity was recorded over both temporal regions. This was more marked on the left than on the right side. (Fig. 6.)

Recording from the depth electrodes in the left amygdaloid region: Spikes were recorded from the depth electrodes, an example of which is shown in Figure 6.

Electrical stimulation findings: This patient was electrically stimulated for a total of seventy-nine times on the fifth, sixth and seventh day after the implantation of the electrodes in the left hemisphere. Positive responses were obtained using 45 and 60 pulses per second, 1 millisecond pulse duration, and 6 to 17 volts. Electrical stimulation reproduced very exactly the patient's clinical behavior. This included "baby talk," grimaces, smacking of lips, gurgling noises, grunts, groans and jerky movements with the hands. In addition, electrical stimulation caused staring, turning of the head to the left, fumbling movements, swallowing, altered breathing, bilateral pupillary dilatation (Fig. 7), 14 to 57 per cent increase in heart rate, and elevation of systolic and diastolic blood pressure from 15/15 to 80/60 mm. Hg. (Fig. 8.) Electrical stimulation caused an after-discharge from the depth electrodes. While the induced electrical seizure pattern was usually associated with a behavioral response, it might occur without any associated clinical manifestations.

COMMENTS

Clinical and physiologic data have been presented in six epileptic patients in whom behavioral difficulties represented a major problem in their management.

From the case histories it is apparent that the types of seizures conformed to the usual patterns of temporal lobe epilepsy, and diagnosis in each case was possible on the basis of the clinical features. Each patient exhibited a variety of attacks. In Case 1, R. B. had minor seizures characterized by brief periods of dazedness, confusion and staring. His major seizures consisted of epigastric and cephalic aura followed

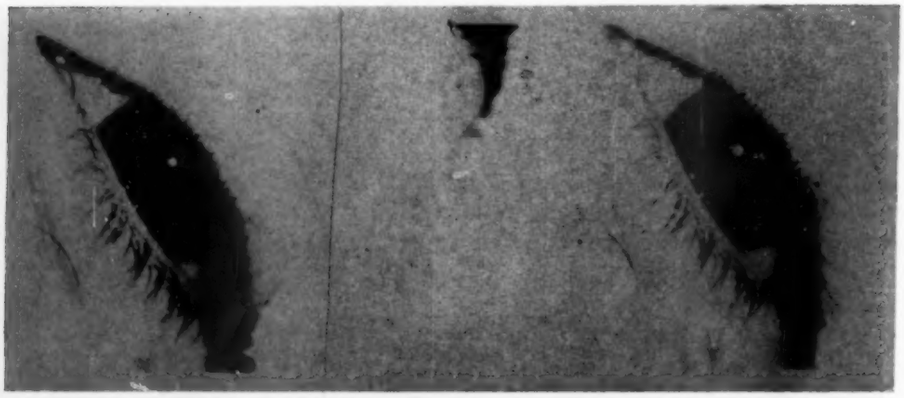

FIG. 7. Photograph of the pupil and palpebral fissure before and during electrical stimulation of amygdaloid region of the left temporal lobe in awake patient M. C. (Case VI) on ninth day after electrodes were implanted. On the left is shown the pupil size and width of palpebral fissure just before electrical stimulation. On the right it can be seen that electrical stimulation with 60 pulses per second, 1 millisecond pulse duration and 15 volts was associated with an increase in pupil size and widening of the palpebral fissure. The pictures were taken with the eye continuously exposed to the flood lights.

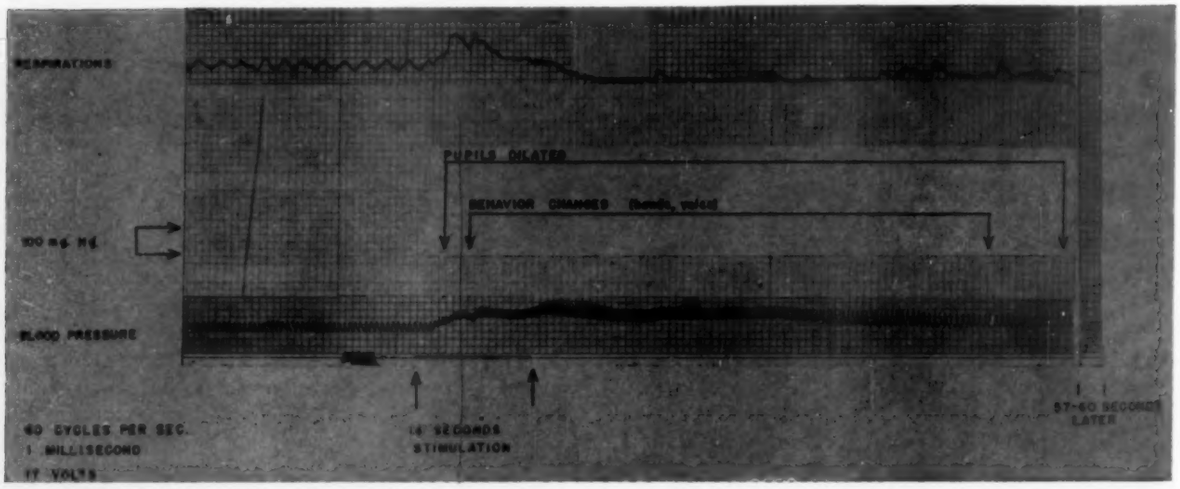

FIG. 8. Electrical stimulation of amygdaloid region in awake patient M. C. (Case VI) eight days after electrodes were implanted. The tracing shows that when 17 volts were used in patient M. C. electrical stimulation first caused a 50 mm. Hg rise in systolic and diastolic blood pressure. Immediately after the end of stimulation the maximal systolic elevation reached 80 mm. Hg and the diastolic elevation reached 60 mm. Hg. Electrical stimulation also produced marked pupillary dilatation and a striking change in mood and motor behavior. The 2.5 second latent period for the initial blood pressure rise indicated a neurogenic mediated response. The continued elevation of the blood pressure with an increase in pulse pressure and the persistent increase in heart rate after the end of electrical stimulation suggested that this phase of the circulatory response was mediated by a humoral substance. An alternative explanation is that the emotional and motor behavior changes produced by stimulation caused a continued neurogenic stimulation to the circulatory system. The behavior changes noted were similar to the attacks of temporal lobe seizures commonly observed in this patient.

by generalized convulsions. In Case II, J. P. had spells characterized by visual and auditory hallucinations, fright, trance-like states with praying, automatism, confusion and amnesia. In addition, he had major convulsive seizures. In Case III, I. N. had minor seizures consisting of olfactory aura alone. In his psychomotor attacks, the olfactory aura was followed by semi-purposive movements, automatism, confusion and amnesia. In Case IV, C. W. had minor seizures characterized by brief periods of dazedness, confusion and staring. Her major seizures consisted of a cephalic aura, followed by generalized convulsions. In Case V, W. C. had minor seizures consisting of swallowing movements alone. In his major attacks the swallowing movements were followed by generalized convulsive movements. In addition he

had spells characterized by violent, destructive behavior and amnesia. In Case VI, M. C. had generalized convulsive attacks and psychomotor attacks. All the patients except M. C. had frequent periods of intractable assaultive behavior either in relation to or unrelated to a seizure. In Cases I, II, IV and V, assaultive, destructive behavior represented a major problem in the management of these patients.

The preoperative electroencephalographic recordings were made with scalp electrodes placed in various combinations over the convexity of the skull. They were abnormal in all the patients. In all six patients the records disclosed spikes over the temporal regions and were thus diagnostic of temporal lobe epilepsy. In addition, in two patients the studies showed abnormalities over the frontal region. We did not use all the special technics that are necessary for the proper localization of the abnormality in the majority of cases [*13,14*]. These technics include the placing of needle electrodes beneath the temporal lobes (sphenoidal electrodes), and a midline basal lead (chin, nasopharyngeal or nasal).

All the patients showed spontaneous spiking from the depth electrodes and one patient exhibited repeated electrical seizure patterns. The frequency and duration of the seizure patterns and spikes, recorded from the depth electrodes, seemed to increase as the electrodes stayed longer in the amygdala. This observation suggests that the presence of the electrodes themselves may have damaged the brain tissue and contributed to the findings. There is ample reason to believe, however, that such damage could not explain all the electroencephalographic findings from the implanted electrodes. This will be discussed at length elsewhere.

Electrical stimulation of the amygdaloid region produced a variety of responses [*15*]. The circulatory, respiratory and pupillary responses have been observed from electrical stimulation of the amygdaloid region in animals [*16,17*]. The subjective and skeletal motor behavioral responses have been reported by Gastaut [*18*] and Penfield [*6*]. In all our patients except one (W. C.) stimulation brought out many of the features of temporal lobe epilepsy such as cephalic aura, fright, euphoria, religious experience, depersonalization, staring, fumbling, fidgeting, swallowing movements, semi-purposive movements of limbs and head, automatism, confusion, unresponsiveness and amnesia. (Table I.) In Case V, there were no responses except for some movements of the patient's right hand and a feeling of bewilderment. In no patient did electrical stimulation produce any response that could be taken for violent or assaultive behavior or a rage reaction. This finding is in contrast to the results of electrical stimulation in animals [*17*].

From our experience of stereotactic positioning of electrodes in the amygdala of cadavers we feel reasonably sure about the position of our implanted electrodes. Verification as to precise location is available in one case only (Case III). This patient had a left temporal lobectomy three months after the depth electrode studies, and the destruction due to electrical coagulation demonstrated that the depth electrodes had been implanted in the lower half of the amygdala just anterior to the tip of the temporal horn and within about 6 mm. lateral to the medial border of the amygdala. Even with precise knowledge of the location of the depth electrodes, as in Case III, we would hesitate to speculate from our depth electrode findings about the relationship of the amygdaloid region to temporal lobe epilepsy. All we can say is that electrical stimulation of this region reproduced certain features common to temporal lobe epilepsy. From these same regions spike activity and electrical seizure patterns were recorded. Our plan of study did not permit us to determine whether or not the placement of the electrodes in adjacent regions of the temporal lobe would have given comparable stimulation and recording results.

The degree and nature of pathologic changes in the brains of our patients is not apparent. They all had a long history of seizures extending over ten to twenty-seven years. Neither the neurologic examination nor the analysis of the cerebrospinal fluid showed any significant abnormality. X-rays of the skull and pneumoencephalograms (obtained in two patients) were normal. All the patients were in the younger age group (sixteen to forty-three years). Macroscopic lesions like tumor, infarct or cyst are unlikely. With the growing practice of temporal lobectomy, it has been found that while some pathologic change is found in all the resected lobes [*12,19–22*], such distinctive lesions are found only in a minority of patients. The majority of patients have lesions with less defined morphology, usually diffuse and only apparent microscopically. They consist mainly of meningeal fibrosis, cellular proliferation in the white matter, sclerosis of the Ammon's horn,

TABLE I

RESPONSES PRODUCED BY ELECTRICAL STIMULATION

Case No., Initials, Age, and Sex	Clinical Features	Electroencephalographic Findings		Electrical Stimulation Findings		
		Scalp, Pre-operatively	Depth Electrodes	Amygdaloid Region Studied	Parameters Giving Positive Responses	Responses to Electrical Stimulation
Case I, R. B., 16 yr. ♂	Minor attacks: brief periods of dazedness, confusion and staring Major attacks: epigastric aura, cephalic aura, generalized convulsions Assaultive behavior following a seizure and unrelated to seizures	Sharp spikes and slow spikes over right temporal region	Spiking	Right	10, 20 and 60 pulses per sec. 1 msec. pulse duration 8–20 volts	Cephalic aura, similar to one before seizure; fright; bilateral pupillary dilatation
Case II, J. P., 37 yr. ♂	Psychomotor attacks: auditory and visual hallucinations, fright, trance-like states with praying, confusion, amnesia Generalized convulsive seizures Postictal assaultiveness	Spikes over both temporal and both frontal regions	Spiking	Left	30 and 60 pulses per sec. 1 msec. pulse duration 10–20 volts	Staring, adversive movements of head and eyes; fumbling; fidgeting; other semi-purposive movements of limbs; religious experience; euphoria; agitation and confusion; unresponsiveness; sweatiness and pallor; tachycardia
Case III, I. N., 43 yr. ♂	Minor attacks: olfactory aura Psychomotor attacks: fumbling, fright, rambling speech, automatism, confusion, unresponsiveness, amnesia Postictal assaultive behavior	Spikes in left temporal region	Spiking and spontaneous seizure discharges	Left	10, 20 and 60 pulses per sec. 1 msec. pulse duration 5–15 volts	Fumbling; fright; depersonalization; confusion; unresponsiveness; adversive movements of eyes and head; tachypnea and tachycardia; rise in blood pressure 50/50 mm. Hg
Case IV, C. W., 28 yr. ♀	Minor attacks: brief periods of dazedness, confusion and staring Major attacks: dizziness, cephalic aura, generalized convulsions Assaultiveness: unrelated to seizures	Spiking over both temporal regions and slow waves over front lobes	Spiking	Left	30, 45 and 60 pulses per sec. 1–2 msec. pulse duration 10–24 volts	Fright; shouting; visual hallucination; confusion; unresponsiveness; tachypnea; bilateral pupillary dilatation; tachycardia
Case V, W. C., 36 yr. ♂	Swallowing movements Generalized convulsions Confusional spells with destructive behavior and amnesia	Frontal spikes and temporal spikes on left side	Spiking	Left	60 pulses per sec. 1 msec. pulse duration 10–20 volts	Semi-purposive movement of right hand; feeling of bewilderment
Case VI, M. C., 27 yr. ♀	Psychomotor attacks: sucking of thumb, clenching of fist, grimacing, confusion, unresponsiveness Generalized convulsive seizures	Spikes over both temporal regions, more marked on the left side	Spiking	Left	45 and 60 pulses per sec. 1 msec. pulse duration 6–17 volts	Staring, turning of head; fumbling movements; swallowing movements; tachypnea; bilateral pupillary dilatation; tachycardia; increase in blood pressure 80/60 mm. Hg; smacking of lips

cortical atrophy and "incisural sclerosis." Until the normal histologic variation is carefully evaluated the importance of such microscopic findings must remain open to question. Crome [*23*] has presented evidence that similar lesions can be found in the temporal lobes of people with no epilepsy.

Very promising results both with regard to relief from fits and improvement of the personality disorder have been reported following temporal lobectomy [*22,24,25*]. It remains to be seen whether or not long-term evaluation will confirm the early promising results. In our cases the follow up has been too short for valid appraisal of the electrocoagulation procedure.

It is hoped that a significant therapeutic result can be achieved by our method of selective destruction of the amygdaloid nuclear region and that extensive temporal lobe surgery can thus be avoided.

The common association of personality disorder with temporal lobe epilepsy has served

to point out the importance of temporal lobes in the integration of personality and behavior. It would be absurd, however, to assume that the anatomic basis of behavior is confined to the temporal lobe or to any one lobe. All we can justifiably conclude is that the amygdala are part of the neurophysiologic unit subserving memory, behavior and personality.

SUMMARY

1. The subject of temporal lobe epilepsy is reviewed briefly.

2. Clinical data have been presented in six epileptic patients in whom behavior difficulties were a major problem in management. A diagnosis of temporal lobe epilepsy was made on the basis of the clinical features and the preoperative electroencephalographic tracings in all these patients.

3. Spiking was recorded from the depth electrodes implanted in the amygdaloid region in all six patients.

4. In all except one patient, electrical stimulation of the amygdala brought out many of the features of temporal lobe epilepsy. Included in the responses to electrical stimulation were elevation of heart rate and blood pressure, pupillary dilatation and changes in respiration.

5. While our current data do not permit us to ascertain the exact role of the amygdaloid region in the genesis of temporal lobe epilepsy, they do suggest that this region is part of the neurophysiologic unit involving temporal lobe epilepsy and behavior.

Acknowledgments: The authors wish to express their appreciation to Drs. H. C. Solomon, Roger Osterheld, J. L. Poppen, G. E. Chatrian, George Geyer, and P. I. Yakovlev for their advice and assistance in these studies.

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Seminar on Atherosclerosis

Current Concepts of Lipide Metabolism*

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In reviewing lipide metabolism it has been necessary to limit the citation of original papers. Frequent reference is therefore made to books [*1–3*] and reviews [*4–12*] on fat metabolism and only those papers which have not been reviewed previously or which for other reasons seem particularly appropriate are quoted directly. I have selected those recent developments which have modified our insight into the mechanisms of fat metabolism and which promise, however vaguely, application to the understanding or management of cardiovascular disease.

Perhaps a few general remarks about recent achievements in the field of lipide metabolism are in order. The organic chemists have given evidence of their ability to imitate and improve upon nature by the synthesis of many naturally occurring lipides and of some that are not found in nature. The biochemists have made headway in elucidating pathways of biosynthesis and oxidation of fats, sterols and complex lipides in intact animals, perfused organs, tissue slices, homogenates, cell fragments and soluble enzyme systems. The more physiologically minded investigators have fought for and gained a foothold in the area of fat absorption, fat transport and fat utilization, and the pathologists have contributed greatly to our knowledge of abnormal lipide deposits in the arteries, liver and other organs. All these groups have been heavily indebted to investigators in various allied fields, in particular to those who provided the technics of chromatography, electrophoresis, ultracentrifugation, histochemistry and the application of isotopes to biologic research.

INTERMEDIARY METABOLISM

Oxidation of Fatty Acids and Cholesterol. Recent advances made in the study of fatty acid oxidation have been reviewed by Green [*5*], Lynen [*6*] and Lehninger [*4*]. These and other investigators have been able to link the stepwise degradation of long-chain fatty acids to the metabolic furnace known as the Krebs tricarboxylic acid cycle. Figure 1 shows in outline form the breakdown of palmitic acid. The free fatty acid, with the aid of adenosinetriphosphate and coenzyme A (CoA), is converted to an activated form which subsequently undergoes a series of reactions whereby in effect hydrogen is removed from the molecule. Finally an activated acetate molecule (acetyl-CoA) is split off and enters the Krebs cycle by condensation with oxaloacetate. The oxaloacetate acts as a carrier since it allows oxidation of the two carbons of the acetate to carbon dioxide and then is itself regenerated to participate once more in the degradation of another acetate molecule. This scheme shows the relation between the metabolism of fatty acid and that of carbohydrate and protein, which also enter the tricarboxylic acid cycle. If by some defect acetyl-CoA accumulates faster than it can combine with oxaloacetate, more acetyl-CoA is diverted to acetoacetic acid and possibly cholesterol, as shown on the left hand side of Figure 1. In the diabetic organism, for example, the accumulation of acetoacetic acid probably results from excessive oxidation of fatty acids [*13*], a block in the synthesis of long-chain fatty acids from acetyl-CoA [*14*] and interference in the oxidation of acetate [*15*].

Apparently all tissues of the mammalian organisms so far examined (liver, kidney, heart, brain, pancreas, muscle, testes and lung) can oxidize fatty acids to carbon dioxide and water. In starvation the heart, for example, depends greatly on a supply of fatty acids for its energy metabolism [*16*]. Thus the view that only the liver is capable of carrying out the initial degradation of the long-chain fatty acid molecule which was previously held is no longer tenable.

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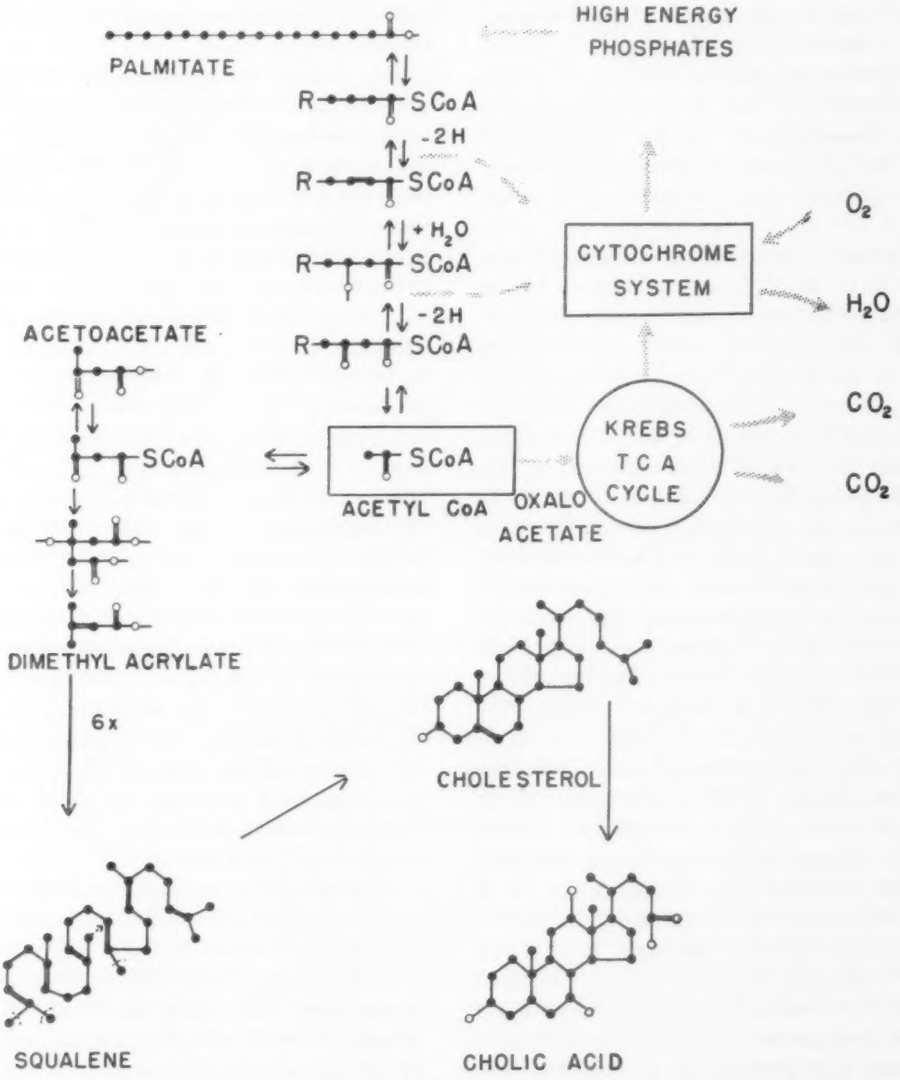

FIG. 1. Schematic presentation of oxidation of palmitate and cholesterol, and of the biosynthesis of palmitate, acetoacetate and cholesterol from acetyl coenzyme A. Only the carbon (•) and oxygen (o) skeletons of the various molecules are shown.

The liver probably differs from other tissues: its rate of fatty acid cleavage to acetyl-CoA greatly exceeds the rate at which these molecules are further degraded to CO_2 and H_2O. Thus the liver is the only significant source of serum acetoacetic acid and other ketone bodies.

The effect of the nutritional state of the organism on the rate of degradation of fatty acid has been thoroughly investigated during the past few years. Liver slices from rats adapted to high fat diets exhibit higher rates of fat oxidation than slices from carbohydrate-fed control rats [*17*]. Similarly, fasting [*18*] and diabetes [*13*] greatly accelerate the oxidation of C^{14}-palmitic acid as demonstrated in liver slices from rats whereas addition to the slice of pyruvate, which is a breakdown product of glucose metabolism, or the injection of insulin diminishes the production of $C^{14}O_2$. *In vitro* addition of glucose to liver slices does not spare fat oxidation although addition of a similar amount of fructose does [*19*]. This apparent discrepancy may be explained by the fact that fructose is more readily utilized by the liver slice than glucose. Apparently the presence of glycolytic products inhibits the degradation of fatty acids and the action of insulin on this process is probably mediated through its stimulation of glucose

metabolism. That the sparing of fat oxidation by carbohydrate must occur during the initial stages of degradation of the long-chain fatty acids is indicated by the fact that the injection of insulin into diabetic rats or the addition of pyruvate to liver slices has no effect on the oxidation of the shorter-chain fatty acid, octanoate [*13,18*].

With the present emphasis on the importance of essential fatty acids as a nutritional factor regulating fat metabolism it is disappointing that so little work has been done on the intermediary metabolism of the essential fatty acids themselves or on their effect on the metabolism of more highly saturated fats. Mead et al. [*20*] showed, however, that the oxidation of fat was not impaired in the intact rat which was deficient in essential fatty acids. Actually, the oxidation of C^{14}-linoleic acid proceeded at a high rate even in the deficient animals, and there appeared to be no mechanism for conserving this essential fatty acid. This study confirms earlier findings that oleic acid is not converted to linoleic acid in the intact organism, but that the latter may be converted to arachidonate. In choline-deficient rats the administration of choline promotes the oxidation of fatty acids as demonstrated in liver slices and certain other extrahepatic tissues [*21,22*]. This finding is consistent with the view that choline prevents the development of a fatty liver by stimulating hepatic fat oxidation rather than by fat transport from the liver [*9,11*]. Cystine and tocopherol, which have received attention in this connection, also stimulate the oxidation of fatty acids [*23*], and it is postulated that normal concentrations of cystine and tocopherol are required to maintain optimal levels of coenzyme A in the liver.

The oxidative degradation of radioactive cholesterol has received renewed attention by the demonstration that ring-labeled C^{14}-cholesterol is not oxidized to $C^{14}O_2$ in a perfused liver whereas the labeled side chain readily releases radioactive carbon dioxide. Apparently the oxidation of cholesterol to bile acids, which is the major pathway by which cholesterol is removed from the body, also takes place in the isolated liver [*24*]. Retarded oxidation of cholesterol may be responsible for the development of hypercholesteremia and atherosclerosis, as is indicated by the greatly reduced conversion of cholesterol to bile acids in dogs receiving thiouracil and cholesterol [*25*]. Other developments in the degradation and synthesis of cholesterol have been reviewed by Friedman et al. [*10*].

Biosynthesis of Cholesterol. A provisional scheme of reactions for the synthesis of cholesterol is indicated in Figure 1. Acetyl-CoA probably condenses to form acetoacetyl-CoA which, with the addition of one more acetyl-CoA and a decarboxylation, gives rise to a five-carbon unit (dimethylacrylate). Six of these five-carbon units condense through various steps to form the long-chain hydrocarbon, squalene. The squalene cyclizes and loses three methyl groups to form cholesterol. A scheme such as this can account for the distribution of C^{14} in cholesterol synthesized from carboxyl- and methyl-labeled acetate [*26*]. Squalene appears to play a role in the synthesis of cholesterol in man. This is demonstrated by the fact that prefeeding of squalene markedly reduces the incorporation of radioactive acetate into serum cholesterol [*27,28*]. Recent evidence indicated that lanosterol is an intermediate in the conversion of squalene to cholesterol [*29,30*] and that demethylation of lanosterol requires the presence of microsomes in the reaction mixture [*29–31*]. It is possible that in the intact cell the major oxidative and degradation reactions proceed with the aid of mitochondria whereas the synthetic mechanisms are carried out by microsomes.

Evidence that cholesterogenesis is controlled by hormonal factors was obtained by the demonstration in liver slices from hypophysectomized rats that little C^{14}-cholesterol from acetate is synthesized [*32*]. This inhibition of cholesterogenesis is not the result of a poor nutritional state of the animal, which similarly will lower cholesterol synthesis. The biosynthesis of liver cholesterol is also regulated by the amount of dietary cholesterol. Thus rats [*33*], dogs [*34*] or rabbits [*35*] fed cholesterol for varying intervals show a sharp decrease in hepatic cholesterogenesis. If such inhibition should also occur in man it would indeed be questionable whether or not restriction of cholesterol intake would have any rational basis; the withdrawal of dietary cholesterol would only stimulate the synthesis of endogenous sterol. That endogenously synthesized cholesterol may be of importance in atherogenesis has been demonstrated in the stilbestrol-treated bird, in which atheromatous plaques develop without the addition of any cholesterol to the diet [*36*].

Tomkins et al. [*37*] studied the effect of other dietary steroids on cholesterol synthesis. Some

steroids reduced the incorporation of C^{14}-acetate into cholesterol of liver slices from rats but neither mixed soybean sterols nor dihydrocholesterol, both of which have been implicated in lowering serum cholesterol levels, had any effect on cholesterol synthesis by the liver. However, Curran and Costello [*38*] found that dihydrocholesterol fed to rabbits or rats suppressed the *in vitro* incorporation of C^{14}-acetate into cholesterol. Apparently, further work will be required to clarify the effects of sterols on cholesterol synthesis.

In view of the commonly accepted importance of cholesterol in the development of atherosclerosis the modification of cholesterol synthesis by physiologic stimuli or drugs might shed additional light on this disease. Thus Frantz and Hinkelman argued that the hypercholesteremic effect of parenteral triton, a surface-active agent, is due to increased synthesis of liver cholesterol [*39*]. Other investigators have found, however, that the increase in blood level might be secondary to alterations in the serum lipoprotein complex and subsequent retention of serum cholesterol [*10,40*]. Accumulation of bile acids in blood also raises blood cholesterol levels. This increase has been explained by "trapping" of plasma cholesterol [*10*], or by increased synthesis of liver cholesterol [*41*], conflicting theories, as in the case of triton. Perhaps this divergence of opinion may be clarified by the work of Hirsch and Kellner [*42*]. These workers showed that mice injected with triton exhibit an increase in total body cholesterol associated with the hypercholesteremia, which therefore cannot be explained by mobilization of cholesterol from the tissues. Their studies on rabbits indicate, furthermore, that triton interferes with the transfer of plasma cholesterol to the liver [*40*]. Since it is already known that triton inhibits lipoprotein lipase by binding serum lipoproteins [*43*] it might be postulated that altered lipoproteins deliver cholesterol to the liver at a slower rate and that this restriction in the supply stimulates liver cholesterol synthesis, as occurs when dietary cholesterol is withdrawn.

Although the majority of investigators have concentrated their attention on the synthesis of cholesterol by liver, extrahepatic tissues such as skin, kidney, testes, adrenal and small intestine also are capable of synthesizing cholesterol [*44*]. Some species differences may exist in this respect: the rabbit [*45*], rat [*45*] and mouse [*46*] apparently synthesize cholesterol in the small intestine very rapidly whereas this is not the case in the dog [*45*]. In view of the immediate involvement of the artery in the process of atherogenesis it is of interest to note that several reports confirm earlier observations on the synthesis of cholesterol by arterial tissue *in vitro* [*35,47,48*]. Cholesterol synthesis in rabbit aorta [*35*] proceeds at the same rate in the cholesterol-fed animals as in control animals although hepatic cholesterogenesis is markedly suppressed by dietary cholesterol. In this respect the rabbit aorta behaves like skin or small intestine of the dog [*34*]. Werthessen et al. [*48*] report conversion of C^{14}-acetate to labeled cholesterol in perfused calf aorta. They show that addition of estrone to the perfusion fluid increases the rate of acetate incorporation. Although these studies indicate that the artery in various species is capable of synthesizing cholesterol, further work on the intact animal is required to determine whether or not this process is important in the development of atheromatous lesions.

The study of cholesterol synthesis from C^{14}- or H^3-acetate in man [*49–53*] shows that injected acetate is rapidly converted to liver cholesterol and that the free cholesterol in the liver equilibrates with plasma-free cholesterol in a matter of hours. Subsequently the free cholesterol of plasma comes into complete equilibrium with that of the red cells. The appearance of cholesterol ester is delayed and the specific activity of this material does not reach a maximum until one or two days after administration of the isotope. Labeled dietary cholesterol appears in the bloodstream much more slowly than cholesterol synthesized from acetate. This may be due in part to the rather slow absorption of exogenous cholesterol but the difference is greater than can be accounted for by this mechanism [*51*]. Probably dietary cholesterol, after entering the bloodstream by way of the lacteals, is rapidly removed by the liver in which it is retained and linked with proteins before release into the bloodstream. These studies indicate that when ingested cholesterol is thus released into the blood its metabolic fate is indistinguishable from that of endogenously synthesized cholesterol.

Biosynthesis of Glycerides. Even if we assume that the fatty acids are synthesized by a reversal of the mechanisms of oxidation, which is at least theoretically possible, we have not yet discussed the manner in which the fatty acids become incorporated into phosphatides and triglycerides. An account of this process has been given by the

studies of Kennedy's group [*54–56*]. These investigators have shown that isolated mitochondria from chicken livers can synthesize lecithin. Apparently, phosphorylcholine is activated enzymatically to form cytidinediphosphocholine. This intermediate then donates phosphorylcholine to a diglyceride molecule like phosphatidic acid and forms lecithin

Cytidine triphosphate — Phosphatidic acid

+ phosphoryl-choline	$-PO_4$
− pyrophosphate	

Cytidine diphosphocholine + α, β-diglyceride
→ lecithin + cytidine phosphate

The role of phosphorylcholine as an intermediate was also demonstrated in mitochondria from guinea pigs [*57*], and a similar system for the formation of ethanolamine-phosphatide has been established [*56*]. In a parallel study Weiss and Kennedy [*58*] demonstrated that chicken liver preparations also catalyze the synthesis of triglycerides by a similar mechanism

palmitoyl-S-CoA + α,β-diglyceride
→ triglyceride + CoA-SH

Thus it appears from these studies that the synthesis of phosphatides and triglycerides is closely related. The incorporation of fatty acids into the lecithin molecule has been greatly clarified by the studies of Hanahan [*59*]. This investigator demonstrated that the fatty acids in the α' position are primarily unsaturated whereas only saturated fatty acids are found in the β ester position. When C^{14}-palmitate was fed to rats approximately 10 per cent of the total lipide C^{14} was found in the lecithin and virtually all of that was recovered in the α' position [*60*]. Thus the two fatty acids of the lecithin molecule may serve entirely different functions, and a minimal intake of dietary unsaturated fatty acids may be required to maintain, by steady turnover, the integrity of tissue phosphatides.

The consensus seems to be that the same conditions which accelerate fat oxidation by impairment in the breakdown of carbohydrate, that is, fasting [*61–64*], diabetes [*65*] or a low carbohydrate diet [*66*], also restrict the synthesis of fatty acids in the animal body. The *in vitro* addition of glucose or glucose plus insulin [*67*] to liver slices from fasting rats greatly enhances lipogenesis. Similar effects are obtained in the isolated perfused liver from diabetic rats [*14*]. The failure of the liver slice from fasting rats to respond to the addition of insulin alone [*64,67*] is probably accounted for by the deficiency of carbohydrate in this preparation. Similarly, the deficient lipogenesis and cholesterogenesis in liver slices from hypophysectomized rats [*68*] is restored by feeding of excess glucose or starch. Most of the previous studies were concerned with the synthesis of total fatty acids of liver in the fasting state but Kline et al. [*69*] studied phosphatide synthesis as well. Phosphatide synthesis as measured by the incorporation of C^{14}-acetate appeared to be diminished but the incorporation of C^{14}-glycerol, C^{14}-glycine or P^{32} was altered only slightly or not at all. Thus it appears that the observed lower incorporation of C^{14}-acetate into phosphatide fatty acid represents a lowered specific activity of fatty acid rather than impaired formation of phosphatide molecules. The accelerated fat oxidation combined with impaired fat synthesis easily accounts for the loss of fat stores when carbohydrate metabolism is disturbed.

METABOLIC CHARACTERISTICS OF FATTY DEPOSITS

Adipose Tissue. The metabolic activity of adipose tissue has not received a great deal of attention although its energy metabolism calculated on the basis of fat-free weight is about one-half that of liver [*7*]. Accumulation of glycogen is observed in adipose cells during the refeeding period after a prolonged fast. This is evidence for conversion of carbohydrate to fat by adipose cells, a conversion that is temporarily blocked by starvation. A very rapid synthesis of fat from C^{14}-glucose by interscapular fatty tissue of mice has also been observed [*46*].

In vitro studies have demonstrated that depleted fat cells eagerly sequester fatty acids from serum [*7*]. Thus depot fat may be synthesized from dietary carbohydrate or fat, which was of course well known before these detailed mechanisms were revealed. In hereditarily obese mice, mice made obese by the injection of goldthioglucose or in obese rats after hypothalamic injury, 90 per cent of the weight increase consists of fat of the same composition as that of normal animals [*70*]. Yet differences in metabolic patterns are seen when these animals are given C^{14}-acetate. In the mice treated with goldthioglucose an increase in lipogenesis is

observed as long as the dietary intake of calories remains high but in the hereditarily obese mice and the obese rats lipogenesis stays accelerated even during periods of negative energy balance [*71*]. Similar experiments [*72*] with C^{14}-palmitate give the impression that obese animals turn over their fat stores at a slower than normal rate.

Fatty Liver. A fatty liver may be produced by excessive mobilization of fat from fat depots by the action of hormones or by neurogenic activity. This type of "physiological" fatty liver is usually associated with hyperlipemia and ketonemia, signs that fat oxidation is accelerated [*1*]. On the other hand, fatty livers produced by liver toxins or by deficiencies of lipotropic agents are associated with normo- or hypolipemia without ketonemia. Studies with radioactive fat have confirmed earlier suggestions that in these conditions fat oxidation is impaired [*21*]. Deuel [*1*] and Best [*8*] have reviewed the action of lipotropic agents in experimental animals and give numerous references to earlier literature. Originally dietary lecithin and, later, choline were shown to be essential for the maintenance of normal liver composition. Soon it became known, however, that the diet does not have to furnish the entire choline molecule if a source of active methyl groups (methionine, betaine) is supplied, and now it is apparent that part of the requirement for active methyl groups may be met by biosynthesis from formate, through reactions involving vitamin B_{12} and folic acid [*8*]. Recent studies have indicated, moreover, that protein deficiency and an improper balance of dietary amino acids result in a fatty liver that cannot be repaired by choline [*8*].

The mechanism of action of choline and other agents in the prevention of a fatty liver is by no means settled. Evidence that choline and certain other lipotropic agents stimulate liver phosphatide synthesis has been summarized previously [*11*]. It appears that lipotropic activity cannot be explained by increased transport of liver fat in the form of plasma phosphatides but it is possible that the increased phosphatide synthesis in the liver is related to accelerated fat utilization by this organ. Certainly liver lecithin synthesis is greatly increased by choline and by other conditions in which fat catabolism is increased [*11*]. Moreover, the more direct evidence that choline stimulates the oxidation of C^{14}-palmitic acid in the liver [*21*] strengthens the hypothesis that this lipotropic agent acts by stimulating the degradation of fat.

Atheromatous Plaques. In the rabbit and chicken a high cholesterol diet is a sufficient stimulus for atherogenesis [*3*]; in the dog, however, cholesterol feeding must be combined with suppression of thyroid activity [*25*] and in the rat the additional factor of cholate in the diet is required [*73*]. Under somewhat different conditions, elevated blood lipides and coronary lesions have been produced in rats on high cholesterol, high fat diets by prolonged exposure to cold [*74*]. The factors required for the production of atheromatous lesions in monkeys have been discussed by Mann et al. [*75*].

In view of all the attention paid to the alteration of blood lipides in both human and experimental atherosclerosis it is somewhat surprising that the chemical composition of the lesion itself has not been more thoroughly investigated. Apart from the observation that cholesterol accumulates in the intima, only sporadic mention is made of the occurrence of abnormally large quantities of phosphatides and triglycerides in this lesion. In our own laboratory we have examined the origin of one group of lipides that accumulate in atheromatous lesions of rabbits, the phosphatides. By comparing the rate of deposition of P^{32}-labeled plasma lipoproteins with the synthesis of phosphatides from P^{32}-phosphate *in situ* it was concluded that practically all excess phosphatide in the artery is derived from synthesis [*76*]. In a later study [*77*] it was demonstrated that the greatly accelerated synthesis of arterial phosphatides is confined to the lecithin and sphingomyelin fractions and that cephalins are not involved. The studies of Steele and Kayden [*78*] confirm earlier findings of Buck and Rossiter [*79*] that sphingomyelin accumulates in human atheromatous plaques. The demonstration that atheroma phosphatides are derived from arterial synthesis rather than from deposition of blood lipids or blood lipoproteins raises some question about the origin of cholesterol and other plaque lipides. Although it has been demonstrated that the artery can synthesize cholesterol *in vitro* the quantitative importance of this mechanism in the production of atheromatous lesions in intact animals has not yet been ascertained.

In the study of experimental atheromatosis major emphasis has been placed on the induction phase and few data are available on the sequence of events after withdrawal of the atherogenic agent. McMillan et al. [*80*] demonstrated, however, that six months after removal of choles-

terol from the diet of atherosclerotic rabbits the cholesterol content of the artery was still maximal although visually the lesions appeared to have regressed somewhat. Similar conclusions were reached by Beher et al. [*81*] who studied the effect of β-sitosterol on the regression of arterial lesions. However, it appears from these experiments that the serum cholesterol level decreases very slowly after withdrawal of dietary cholesterol. It takes more than a month for the extreme hypercholesteremia to decrease 50 per cent, and even after four months the serum cholesterol level is still elevated. It is therefore not too surprising that atheromatous lesions persist. A more interesting question is: Why does the hypercholesteremia persist so long? Is there enough cholesterol stored in the liver to maintain a constant oversupply to the plasma? This does not appear too likely. Perhaps the hypercholesteremic rabbit suffers from a metabolic derangement in the removal or degradation of body cholesterol, as was observed in the dog [*25*]. Only further study will clarify this situation.

In discussing the effect of cholesterol or dietary fat on atherogenesis most students of this disease assume that the dietary lipide is directly responsible for the accumulation of lipide in the artery or that it causes some metabolic derangement in lipide metabolism which then causes the arterial lipoidosis. Yet it would seem entirely possible that dietary lipide triggers the development of arterial lesions in a much more indirect manner. One such mechanism has been reviewed and discussed by Fullerton [*82*] who accepts the earlier hypothesis [*83*] that the formation of fibrin and its deposition in the arterial wall represents the earliest phase in the development of atherosclerosis and that fatty changes in the artery follow. It has been shown repeatedly that phosphatides [*11,84*], free fatty acids [*85*] or chylomicra [*86*] promote the coagulation of blood. The presence of excess fat in the bloodstream would thus promote thrombogenesis [*87*] and perhaps also the infiltration of the fibrin-induced lesion with lipide [*88*]. Such a sequence of events might elucidate the correlation between the incidence of atherosclerosis and of various types of lipemias. A somewhat different although related approach has been taken by Swank [*89*] who has shown that the presence in blood of chylomicra from dietary fat or from intravenous fat emulsions greatly increases the viscosity of blood. Such a change in viscosity with a resulting slowing of blood flow, coupled with an increased coagulability of blood induced by chylomicronemia, might constitute the causal link between increased blood lipide concentrations [*90*] and the final thromboembolic event in the coronary patient.

LIPIDE TRANSPORT

Since serum lipoproteins and the hormonal and dietary control of serum lipides will be reviewed in future articles in this series, these topics will be omitted from the present discussion.

Absorption of Lipides. Present concepts of the mechanisms of digestion and absorption from the gastrointestinal tract have been reviewed by Bergström and Borgström [*12*]. The differences of opinion between supporters of the lipolytic and partition theories have not been resolved. According to the former school, fats are completely split in the intestinal tract, resynthesized and transported by the lymphatics, whereas the supporters of the latter view hold that little splitting goes on in the gastrointestinal tract and that most of the fat is absorbed as intact fat droplets. Perhaps the views of Reiser and Dieckert [*91*] might serve as a compromise. These investigators believe that their experiments with doubly labeled triglycerides show a splitting of 60 per cent of the triglycerides to monoglycerides, absorption of these molecules, resynthesis without participation of intestinal phosphatides, and transport by the thoracic duct. These concepts are supported to some extent by the work of Gidez and Karnovsky [*92*] who studied the absorption and metabolism of the glycerol moiety of glycerides. When glycerol-labeled triolein is fed to rats, complete absorption occurs in four hours. The specific activities of various glycerides in the intestinal wall indicate that most of the fat is absorbed prior to complete hydrolysis. A somewhat similar conclusion was reached for the absorption of phosphatides. Studies with P^{32}- and C^{14}-labeled phosphatides show that the rat absorbs a significant portion of fed phosphatides without hydrolysis [*93–95*].

The lack of effect of fat absorption on the turnover of intestinal phosphatides has been repeatedly demonstrated [*11*]. Similarly, during fat absorption the triglycerides in intestinal lymph increase much more than the phosphatides [*96,97*]. Thus it is becoming more and more evident that, although phosphatides may aid the transport of absorbed lipide, nearly all the fat is transported in the form of triglycerides.

The application of balance experiments to study fat absorption in man or experimental animals is limited by the circumstance that an unknown quantity of fat is secreted into the intestine. Thus Tidwell et al. [*98*] observed in the intestinal contents a decrease in specific activity of fed C^{14}-palmitic acid diluted with olive oil, which was interpreted as dilution of the oral dose by secreted fat. Unfortunately this is not conclusive evidence since Borgström demonstrated that after feeding C^{14}-palmitic acid diluted by corn oil the specific activity of fatty acid in lymph early in the experiment is twice as high as that of the oral dose. Apparently the free fatty acid is preferentially absorbed from the fat mixture, leaving behind a residue of lower specific activity [*99*]. Although C^{14}-labeled fats have been used profitably in animal studies the inherent dangers of this isotope have limited its application to man. It is fortunate, therefore, that one can label various fats with radioactive iodine (I^{131}). By this means Malm et al. [*100*] were able to demonstrate in normal subjects a more rapid absorption of I^{131}-olive oil than of I^{131}-oleic acid. About 70 per cent of the I^{131} of the administered olive oil is excreted in the twenty-four-hour urine, indicating rather rapid deiodination of the radioactive fat. Of course, it is too early to tell whether or not the deiodination is a reliable index of fat oxidation. Patients with previous gastric surgery or pancreatic disease [*101,102*] show smaller amounts of I^{131} in their blood and larger excretion of I^{131} in the stool after a single dose of oral I^{131}-triolein than normal control subjects. Thus triolein apparently is not deiodinated in the intestine.

Although it is commonly accepted that bile is required for the absorption of lipides from the gastrointestinal tract it has been suggested that steatorrhea in animals or in patients with bile fistulas is the result of increased secretion of fat into the intestine rather than decreased absorption [*103,104*]. One might expect that the application of radioactive isotopes would elucidate this problem and, indeed, the observation [*105*] that obstruction of the common bile duct in dogs does not diminish the entry into the blood of I^{131} from orally administered I^{131}-triolein lends support to this suggestion. Similarly, labeled phosphatides [*106*] and labeled fatty acids [*99*] appear to be adequately absorbed in rats with bile fistulas. However, it was observed that only one-fourth of the normal amount of free fatty acid or phosphatide appears in the intestinal lymphatics. Thus bile might regulate the path by which lipides are absorbed rather than the quantity which is assimilated. In view of these findings Siperstein et al. [*107*], who measured the absorption of lipides on the basis of collected lymph, may wish to review their opinion that bile is required for the adequate absorption of fatty acids.

The demonstration that plant sterols lower the serum cholesterol level in birds [*108*] prompted numerous studies on the mechanism of sterol absorption and possible ways of interfering with this process. Rats given 1 to 20 per cent D-labeled cholesterol absorb about 45 per cent of sterol until the dietary cholesterol level reaches the 10 per cent level at which time the per cent absorption decreases [*109*]. This observation agrees with the findings of Ivy et al. [*110*] who compared the absorption of cholesterol with dihydrocholesterol and soybean sterols. Although the latter two types of sterols appear to compete with cholesterol for absorption, the exogenous sterols do not seem to increase the elimination of endogenous cholesterol. From the literature it cannot be ascertained whether soybean sterols or other sterol analogs are effective inhibitors of cholesterol absorption. According to Hernandez et al. [*111,112*] the appearance of fed C^{14}-cholesterol in thoracic duct lymph of rats is greatly reduced by the simultaneous feeding of mixed soybean sterols or β-sitosterol. However, the results from Friedman's laboratory [*113,114*] appear to be in direct contradiction to these findings. After prolonged feeding of plant sterols, rats may absorb as much as one-fourth of the fed sterols [*110,115*]. Even though no plant sterols are found in the blood or liver of these animals the blood cholesterol levels are increased above normal [*115*]. Some of these contradictory findings may be due to the difficulty in the determination of cholesterol in the presence of other sterols. Wider application of chromatographic technics [*115*] would appear desirable. Further studies of dosage, type of sterol preparation, method of administration and the presence of accessory dietary factors may eventually unravel these controversies.

Even though cholesterol is absorbed in the absence of dietary fat the balance of evidence shows that certain dietary fats promote cholesterol absorption [*116*]. In man, for example, cholesterol from eggs, which is intimately mixed with triglyceride and lecithin, produces more

hypercholesteremia than the same amount of crystalline cholesterol [*117*]. Some investigators believe that esterification of cholesterol is involved in the absorption of dietary cholesterol [*118*] and that dietary fat promotes cholesterol absorption by providing fatty acid for esterification as well as by stimulating the flow of bile, which in turn activates cholesterol esterase. The importance of esterification for cholesterol absorption, however, has been questioned [*119,120*].

Origin and Fate of Plasma Lipides. It seems fairly well established that in both the fasting rat [*121,122*] and dog [*9,123*] the liver plays a pre-eminent role in the production and utilization of plasma phosphatides and cholesterol. This is somewhat surprising since studies with P^{32}-, C^{14}- and H^3-labeled lipides or lipide precursors have revealed that most tissues of the mammalian organism can and do synthesize phosphatides [*9*] and cholesterol [*44*]. In the chicken [*124*] and rabbit [*125*], however, extrahepatic tissues appear to contribute appreciable quantities of phosphatide to the bloodstream. Moreover, in the latter two species the plasma phosphatides contain a much greater percentage of cephalin than in either man, rat or dog. Quantitative aspects of cholesterogenesis in intact animals and in man have already been referred to in the section on cholesterol biogenesis. Two studies on phosphatide transport in man should be mentioned, however. Moser and Emerson [*126*], in a careful study, calculated the turnover rate of phospholipide in the liver and plasma compartment and found that the turnover time in normal man ranged from sixty to ninety-five hours, or an absolute turnover rate of about 18 gm. per day. When we compare this to the turnover of 1 to 3 gm. per day of a similar pool of cholesterol [*53*] it is evident that the plasma phosphatides are renewed much more rapidly than cholesterol. Similar studies in nephrotic patients show that in nephrosis the exchange of phosphatides between tissue cells and plasma is slower [*126*]. Florsheim et al. [*127*] compared the disappearance of injected labeled phosphatides from the bloodstream with the synthesis of newly formed plasma phosphatides from P^{32}. Both technics give comparable answers and show little or no difference in the absolute turnover rates of plasma and liver phosphatides in various thyroid states.

The role of the reticuloendothelial system (RES) of the liver in the removal of lipides from the blood has been emphasized by Friedman et al. [*10*]. In a series of papers on this subject they show that in rats or in dogs treated with so-called RE blocking agents the removal of chylomicra and of exogenous cholesterol from the bloodstream is impaired whereas endogenous cholesterol continues to be removed. Exogenous cholesterol was found in isolated Kupffer cells and in RE cells *in situ*. According to these authors, dietary cholesterol enters the bloodstream primarily as a part of chylomicra, the chylomicra are absorbed by liver RE cells and the cholesterol is then released as "endogenous" cholesterol. The ease with which hypercholesteremia develops in the cholesterol-fed rabbit is ascribed to the relative sluggishness of rabbit liver RE cells* [*128*]. A critical discussion of these interesting results is beyond the scope of this article. It should be pointed out, however, that it is debatable whether or not RE block can be achieved by the methods employed. Since a major portion of the argument for RES participation in lipide metabolism depends on the assumption that RE block was achieved, one might wish some proof of this hypothesis.

Mechanisms of Hyperlipemia. The term hyperlipemia or lipemia is used in a number of different ways and the manner of usage is not always clear. It would seem that (hyper)lipemia might be properly used when one wishes to convey the idea that the total lipide content of the blood is above normal limits. If one discusses the elevation of only a single type of blood lipide one might preferably use the terms (hyper)phospholipemia, (hyper)cholesteremia and (hyper)-triglyceremia. In addition, if one wishes to refer to an excess of chylomicra in the blood one might reserve the term (hyper)chylomicronemia. In the present discussion this terminology will be followed.

The studies of Ahrens and Kunkel [*130*] led to the suggestion that blood serum from patients with elevated blood lipide levels failed to show turbidity when the serum phosphatide concentration was relatively high. Albrink et al. [*131*] indicate, however, that the turbidity of serum is more related to the neutral fat content of the

* A different view has been expressed by French et al. [*129*] who observed that the lipide particles of plasma from rabbits fed cholesterol contained a relatively large proportion of cholesterol that resisted clearing by post-heparin "clearing factor," and inhibited the clearing of fatty chyle. Thus the removal of lipide from hypercholesteremic rabbit serum may be impeded by a partial block in the clearing mechanism.

blood, irrespective of its phosphatide content. The latter investigators state that whenever the neutral fat content of the blood exceeds 20 mEq./L. (590 mg. per cent), lactescence is present. Thus it appears that some neutral fat is held by serum proteins in more or less "soluble" form, whereas when the proteins are saturated we find "insoluble" fat which can be removed by high speed centrifugation. The lipide composition of lipoproteins from fatty chyle and serum were also compared [*132*]. These analyses show that the chyle lipoproteins are much richer in triglyceride than serum lipoproteins and suggest a preferential rapid removal of triglycerides from the bloodstream.

Friedman and Byers [*133*] studied the role of phospholipemia and triglyceremia in the genesis of cholesteremia. They show that continuous infusion of phosphatide or triglyceride emulsions into rats causes a marked increase in the serum cholesterol level. This effect is observed even in the absence of the liver [*134*]. The authors make the interesting observation that, since the serum cholesterol level apparently can be manipulated by alterations in serum phosphatides or triglycerides, the fundamental disturbance in some types of clinical hypercholesteremia may not reside in a primary abnormality of cholesterol metabolism but may be the result of a failure of glyceride synthesis or degradation with a secondary change in serum cholesterol level. Another instance of hypercholesteremia apparently induced by a primary defect in some other serum constituent was described by Rosenman et al. [*135*]. The elevated serum lipide levels in rats with experimentally induced nephrosis seem to be related to the loss of serum albumin. In this connection it is interesting to note that hyperlipemia fails to develop in bilaterally nephrectomized dogs when the serum solutes are maintained near normal levels by peritoneal lavage [*136*].

Lipemia Clearing Factor. Even more important than the problem of producing hyperlipemias is the question of how to reduce them. Certain aspects of this question will be discussed in future articles dealing with serum lipoproteins and the control of serum lipides by diet and hormonal preparations. However, one aspect of this problem, reviewed by Bergström and Borgström [*12*], deals with lipemia clearing factor and has led to a modified concept of lipide transport. The discovery that heparin abolishes alimentary lipemia was followed by the isolation of a lipoprotein lipase which hydrolyzes the triglyceride of soluble lipoproteins, chylomicra and of artificial fat emulsions activated by α-lipoprotein [*137*]. The lipoprotein lipase probably acts primarily in or at the surface of tissue cells but it may spill over into the plasma after the administration of heparin or in the presence of hyperlipemia. It now appears that lipoprotein lipase may be a normal, physiologically active enzyme which catalyzes the removal of triglycerides from the blood. Grossman et al. [*138*] observed that in man, alimentary lipemia or lipemia following the intravenous administration of fat emulsions is associated with an increase in unesterified (or free) fatty acids in serum. Similar increases have also been reported in fasting subjects [*16,139,140*] and in patients with diabetic acidosis [*140*], whereas a decrease occurs when carbohydrate utilization is increased by administration of glucose [*16,139*] or insulin [*140*]. The lipolysis of triglycerides by lipoprotein lipase is associated with increased oxidation of triglyceride fatty acids, as shown by the increased output of $C^{14}O_2$ in rats given a radioactive soybean oil emulsion and heparin intravenously [*141*]. Thus we may infer that lipoprotein lipase progressively removes triglyceride from the microscopically visible chylomicra as well as from the more soluble lipoproteins, and that the liberated fatty acids are carried by serum albumin until they can gain access to the intracellular oxidation systems. There are, however, a number of questions left to be answered, and it is not certain that this mechanism can account for the rapid rate at which triglyceride passes from the circulation through the capillary endothelium into the tissue cell.

CONCLUSIONS

The role of the lipides in the total body economy cannot as yet be convincingly defined. Undoubtedly the fact that the caloric value of triglycerides is high and that triglycerides may be deposited in a water-insoluble state makes them an important form of energy storage. However, this property of insolubility in aqueous media imposes difficulties in penetration and transport which require the participation of a phosphatide-cholesterol-protein complex, as well as of hydrolytic mechanisms such as pancreatic and lipoprotein lipase. There is a possibility that phosphatides play a role in the oxidation of triglycerides and their presence in large quanti-

ties in the nervous system makes one suspect that they participate in the execution of nerve function. Their participation in secretory mechanisms also has been suggested [*142*]. Cholesterol probably serves as a precursor of various steroid hormones and bile acids which in turn play a role in the absorption of cholesterol and other lipides. Whether or not cholesterol is directly involved in the etiology of atherosclerosis and whether or not this mechanism should be listed as a "function" of cholesterol is, in the opinion of this reviewer, somewhat questionable.

Acknowledgment: The author gratefully acknowledges the assistance of Mrs. Alma Sutton in the preparation of the bibliography and the illustration.

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Conference on Therapy

Drug Reactions

These are stenographic reports, which have been edited, of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors.

Dr. Harry Gold: The conference this afternoon will be opened by Dr. Cattell, of the Department of Pharmacology.

Dr. McKeen Cattell: The problem of drug reactions is one of great concern to physicians. As an introduction to the discussion of the aspects met with in clinical practice, I would like to say a few words regarding the nature of the problem. Under appropriate circumstances any drug may give rise to untoward effects or, as we often call them, side actions. When this happens unexpectedly, there is a tendency to hide our ignorance by saying that the patient has an idiosyncrasy to the drug. It is worth while to consider the problem of individual variation in relation to the occasional or unexpected toxic reaction. Why is it that now and then a patient reacts in an unexpected manner to the usual dose of a drug?

It is obvious that the answer to this question is at least in part related to the problem of individual variability, and it is of interest to inquire to what extent this factor may be implicated in the occasional reactions which are of special concern to us. Variability, of course, is characteristic of biology. No two individuals are exactly alike, and in the same sense we find that no two individuals react to a drug in exactly the same manner. There are always quantitative differences in the response. The problem is similar to that of the probability curves which you are familiar with, for example, the distribution of numbers in the throwing of dice and the chance of a given number turning up a certain number of times. This, when charted, is called the normal curve of variation. This type of curve is familiar to all of you I am sure and represents what we speak of as the normal distribution curve. No matter what characteristic is studied, a certain mean value will be found around which the data will fall.

Let us now refer specifically to the reactions produced by a drug. The mean dose is indicated by the vertical line which cuts through the dosage-response curve near its peak. It marks the dose which is effective in 50 per cent of the population under study. It is commonly called the E.D.50. A certain number of persons will respond to a relatively small dose, while others require a fairly large dose before the effect is obtained.

There is also the other aspect of the problem to consider, that is, the toxic dose, which has a similar distribution curve. In the case of experimental work in animals, we commonly use the dose which causes death. This is the L.D.50.

The problem in dealing with therapeutic agents is the separation of these two curves. This separation is not always cleancut and, in fact, with a distribution curve of this type it is probable that a certain proportion of the population will deviate rather widely from the mean. We are particularly concerned with any overlap of the effective dose with the lethal dose—a circumstance which occurs every now and then in connection with the therapeutic use of drugs.

The question arises as to the incidence of toxicity which is allowable in relation to any given type of medication. Of course, that is determined largely by the purpose for which the drug is being employed. If one is concerned with a serious disease, a drug could be used which has a much greater potential for harm than in the case of some minor condition. This factor needs to be considered in the therapeutic use of any drug. The problem has been examined by the late Dr. Clark, who was Professor of Pharmacology at Edinburgh. He suggested that one death in a thousand would be too high under most circumstances and believed that something like one in ten thousand would be more reasonable for a therapeutic agent. Again, the figure that one would accept would depend upon the

seriousness of the condition being treated and the availability of other drugs for the same purpose.

Dr. Clark's successor at Edinburgh, Dr. Gaddum, is visiting this country and is in the audience. Dr. Gaddum has contributed a great deal in the analysis of data of this type and I hope he may have a few words to say.

This curve is familiar in experimental studies on the toxicity of drugs in animals. As an example, we may take digitalis, because ample data are available from the assay of digitalis preparations in the cat. Some animals die of a rather small dose and others of a relatively large dose. In this instance the smallest dose which kills an animal is about one-fourth the amount which kills all. In other words, there is a fourfold difference between the dose of digitalis which kills all the animals and that which kills one. This represents one of the least variable instances we have in the general population. Particularly when we are dealing with patients with disease, the variability is very much greater and, as Dr. Clark pointed out, under these circumstances it is to be expected that an occasional person can be expected to vary widely from the average and may respond with an unexpected reaction. Thus an unexpected response, described as an idiosyncrasy, might well be a normal response to the action of that drug in a particularly susceptible patient. This might be true even if it happened only once in 10,000 times.

There is another type of side action which differs qualitatively from those of the usual pharmacologic actions of the drug and which is peculiar to the individual; a reaction which may more properly be termed an idiosyncrasy, since it is a type of reaction not shared by the population as a whole. In general these qualitative abnormalities in response form the group which we speak of as allergic reactions. They include such effects as urticaria, hay fever, possibly leukopenia and some of the other blood dyscrasias. Why certain persons should respond in this way and others not is of course something we would like to know. It is said that approximately 10 per cent of the population is subject to reactions from environmental factors such as food, inhalants and other materials, but we cannot say why.

The evidence relating to the type of compound which may cause allergic reactions is in an equally unsatisfactory state. We know that such drugs as acetylsalicylic acid, thiouracil, the organic arsenicals and sulfonamides, to mention a few, are much more likely to offend than certain others such as alcohol and digitalis. Pharmacology provides but few grounds for predicting the probability of development of an allergy to a compound, although it occurs more frequently with certain types of compounds than with others.

A minor change in the chemical structure often results in a compound which produces a much lower incidence of allergic reactions. There are, of course, many groups of drugs in which little is known of the relationship between the action of the drug and its chemical structure.

It seems probable that a number of reactions may depend upon effects which are basically allergic or non-allergic in character, and the question arises how these may be distinguished. The following criteria have been suggested by Dragstedt: First, the type of reaction. If the pattern is consistent with known manifestations of allergic agents, such an urticaria, dermatitis, angioneurotic edema, asthma or fever, then it is more likely to have an allergic basis. Other responses to drugs, such as jaundice, liver atrophy, optic atrophy, and the like, are probably not often allergic. Certain others, including granulocytopenia, anemia and thrombocytopenia, may be of either type, that is, due either to a direct action of the drug or to an acquired type of allergic response.

The second point Dragstedt makes is the dependence on sensitization. The reaction occurs only after a second or prolonged course of therapy, that is, it takes time to develop. If the reaction no longer occurs when the dose is moderately reduced, it is probably not allergic. An individual who is sensitized to a drug commonly responds to a dose which is minute in terms of the therapeutic dose.

The third characteristic of an allergic reaction is the relief that is obtained by antiallergic agents. If the symptoms are relieved by known antihistaminic compounds, including epinephrine, then the reaction is probably due to an allergy. The subject requires more study, and at present we are often unable to say in which category the reaction falls.

I will leave off here and hope that some other points may be brought out in the discussion.

DR. GOLD: Thank you, Dr. Cattell. Dr. Barr, could we have some comments from you?

DR. DAVID P. BARR: Dr. Gold, I was attracted by the title of our conference today because of my interest in mishaps and catastrophies from

the clinical use of diagnostic and therapeutic agents. In the aggregate, the dangers and damage are appallingly great.

During the past year we have recorded all instances of major toxicity and accidents that have occurred in our wards. Some developed before the patient entered the hospital; others after the patient's admission. Some resulted from the use of accepted dosage of drugs in unusually susceptible patients. In the group of accidents, we saw infections introduced by puncture with a needle or by procedures employed in diagnostic investigation of the urinary tract. We encountered many allergic reactions. We observed damage that resulted from changing the internal environment of the body, an example being disturbance of homeostatic mechanisms by combinations of diuretic agents such as diamox,® mercurials and ammonium chloride with a salt-poor diet in the treatment of heart failure. This developed in association with the use of digitalis or without it. We found that alterations in the internal environment might produce toxic reactions to digitalis with doses usually regarded as safe and therapeutic.

The danger from use of diagnostic and therapeutic agents arose not so much from the risk involved in each agent, but from the multiplicity of measures that were used. We now have so many remedies that may be helpful—a possible remedy for each symptom—and the sum of symptoms is often great in the individual patient. In one patient, during a sojourn of four weeks in the ward, as many as twenty-eight drugs and thirty-five diagnostic tests were used. From the point of view of danger, this treatment may be regarded as involving sixty-three possible insults.

From our survey, we have arrived at certain generalizations. One is that in any medical ward at New York Hospital iatrogenic disease constitutes one of the most frequent diagnoses. Another is that no diagnostic or therapeutic measure is without its own particular danger. For each, the risk may be small but the sum total of small risks may be large. When we look over the list of possible untoward effects we may be surprised that man-made disease is not even more frequent or that any patient escapes from our wards without some damage.

In the review of our cases we noted that the great majority of accidents occurred with proper use of drugs, and when the calculated risks justified usage. In other instances, unfortunately we were forced to admit that the agent or procedure was used unnecessarily. A dreadful example was a fatal accident following the use of decholin® as a measure of circulation time. The drug was introduced intravenously in the usual way in the study of a girl who had a history of asthma. The physician who ordered it gave it because he wanted to be complete and thorough in his examination. There was actually no other assignable reason for measurement of circulation time. Ten minutes after the decholin was introduced the girl was dead from anaphylactic shock.

I published recently a short article on this subject. I hoped then, as I do today, that my emphasis on danger would not be misinterpreted. I have not become a diagnostic or therapeutic nihilist and I thoroughly believe in the great value of modern therapy and the brave use of diagnostic measures. Nevertheless, I am more and more convinced that lack of discrimination in trying to be thorough constitutes a frightful danger. Every agent used in the care of patients should be submitted to rigid scrutiny. First, to determine whether or not its use is strictly necessary, and second, to ascertain whether or not the risk of using it is justified by the possible benefit.

DR. GOLD: Thank you very much, Dr. Barr. That was a statement that needed to be made. We do not get any such impression from the circulars that come in the mail every morning.

DR. CATTELL: May I call attention to Dr. Barr's paper which was published in the December 10 issue of the *Journal of the American Medical Association?* There you will find a searching analysis of this problem. I believe that in the sample population studied you came out with a figure of a 5 per cent incidence of man-made illness.

DR. BARR: That is correct. Analysis for a second year corresponded closely to the published results. In the estimate of 5 per cent, we did not include a case of cinchophen poisoning that came to us from a misguided practitioner who destroyed his patient's liver by the unnecessary and unjustifiable use of that drug. We included no example of nostrum administration or the use of drugs that were not recognized. We tried to make each example represent, as far as possible, the conscientious efforts of a good physician to aid his patient.

DR. GOLD: The actual incidence of these accidents, then, is really higher than appears

from your study, and further emphasizes its importance.

Dr. Cattell mentioned the fact that Dr. Gaddum of Edinburgh is here. We might be privileged perhaps to have a few words from Dr. Gaddum.

DR. J. M. GADDUM: Dr. Cattell seemed to expect me to say something about these dosage-response curves and if you like I will, but I do not know whether or not anyone else will be interested to hear me. These curves are useful because they tell all you really want to know about the variation of people, the probability of obtaining a particular effect from a given dose. The curves are easy to determine. All that is required in order to get not only the position of the middle of the curve but also its width is to try two different doses and measure the percentage of positive effects with each dose. The results are plotted on logarithmic probability paper and the curve tells how much the subjects varied. It is so easy to do that I believe it ought to be done more often. I cannot guarantee that the curve will always be the right shape exactly, but it nearly always is. It is thus very easy to measure the variability of the population.

If there were more data in the literature concerning the slopes of the curves from the results plotted that way, it would interest me and should be of interest to other people. I think this variability is an important factor because the safety of using a drug depends on its magnitude. We do not know nearly as much as we should about the relation between the structure of a drug and the variability of the response.

DR. GOLD: Thank you. The subject is now open for general discussion. Are there any questions anyone would like to put to Dr. Cattell?

DR. JANET TRAVELL: We have not heard anything about the influence of psychologic factors on pharmacologic effects, the negative and positive placebo reactions. We had a patient last week on whom we wished to start a controlled study. We gave the patient some vials of sterile saline, marked "New drug for investigational use," and after the first dose the patient was brought to the emergency ward of the hospital almost in a state of collapse, with acute anxiety over the effects of the new drug. I would like to hear Dr. Gold's comments on this situation.

DR. GOLD: I would like to turn that question over to Dr. Modell.

DR. WALTER MODELL: A paper or two has been published by Stewart Wolf citing a long list of so-called toxic reactions from dummies, as Dr. Gaddum would like to call them. I think it is an important point to be considered in evaluating drugs.

DR. GADDUM: An extremely interesting paper was published in which all the patients who responded to dummies were excluded and then the results obtained on the other patients really meant something, whereas when all the results were put together they had no statistical significance.

DR. GOLD: Have you encountered toxic reactions with dummies?

DR. GADDUM: Not in my own work but I have come across it in the literature frequently.

DR. GOLD: I think I mentioned at one of the previous conferences that we once encountered a fairly advanced grade of addiction to a placebo.

DR. GADDUM: May I say a few words on the use of the word "placebo?" I think the placebo is something to give in the therapy of the patient, but when dummies are given it does not give pleasure. If we call it a dummy when it has the effect of improving the patient, it thereby loses some of its effectiveness as a control because it is acting as a placebo. I think perhaps I am making a fuss about a small point which is not very important, but I like to distinguish between dummies which are used for scientific purposes and the placebo used with the intention of producing psychologic effects.

DR. GOLD: I was wondering how sharp such a distinction could really be, because whenever a patient is given medicine it can have only one of three results: either it does nothing, makes him worse or makes him better. What it does depends, not entirely upon what the doctor wants to do about it, but how the patient reacts. So I was wondering how useful is this placebo-dummy separation.

DR. GADDUM: If you try to exclude the therapeutic suggestion, it is a dummy. If you use it for the purpose of impressing the patient with the fact that he is going to get better, it is a placebo. Perhaps it is a matter of words.

DR. SOLOMON GARB: I wonder if the figures which Dr. Barr gave us referred only to the toxic reactions which occurred in the hospital or did they also include any delayed events that may have occurred after the patient went home from the hospital?

DR. BARR: Everything described in our publication occurred while the patient was under observation in the hospital although, as already

mentioned, many of the toxic reactions had begun before the patient was admitted to the ward.

DR. GARB: As I recall, in your address that was published in the *Journal of the American Medical Association* you suggested the possibility that there are some diseases which we have looked upon as naturally occurring which may in effect be iatrogenic, but we have not recognized them as such. Would that then increase the probable actual incidence of toxic reactions?

DR. BARR: I think so. That is an interesting speculation. With apresoline,® for instance, it is quite possible to produce a syndrome that is almost indistinguishable from lupus. It happens to be temporary, but it has the same systemic manifestations, joint afflictions, depression of the white blood cell count, fever, and even lupus cells. Through the work of Rich it appears that sulfonamides or foreign serum may produce an effect closely resembling periarteritis or polyarteritis nodosa. Also it seems to me interesting that one can with some of the newer tranquilizing drugs produce a syndrome which is sometimes quite similar to paralysis agitans. One thinks also of the action of lysergic acid in causing effects not unlike the symptoms of dementia praecox. Some drugs produce a single recognizable reaction, others several toxic manifestations. It is possible that a few produce complete syndromes of diseases.

DR. GOLD: Dr. Cattell, in regard to terms, am I correct in understanding that you were trying to distinguish hypersensitivity from allergy or idiosyncrasy; that is, the label, hypersensitivity, is used to describe the individual's variation within the framework of the basic action of the drug, and that idiosyncrasy or allergy refers to a reaction which lies outside of that?

DR. CATTELL: Yes, qualitatively different and not shared by the general population.

DR. GOLD: I want to be sure you intended to make that distinction, that it is correct.

DR. CATTELL: Yes.

DR. MARY LOVELESS: That would be confusing in relation to the terminology used by the allergists. I would rather use hyper-responsiveness for an increased or exaggerated pharmacologic effect and call hypersensitivity an allergy, something qualitatively different.

DR. CATTELL: I agree with Dr. Loveless. Since the term "hypersensitivity" has a special connotation in relation to reactions to pollens and the like, it seems to be preferable not to use it.

DR. GOLD: Hyper-responsiveness?

DR. CATTELL: Not necessarily. We are concerned with the end of a scale indicating a relatively high susceptibility of a population to a drug. These are persons who are more sensitive than the average to a drug. Perhaps low threshold would be an appropriate term.

DR. GOLD: I was struck by the example Dr. Cattell used in regard to the range of variation, that of digitalis. As Dr. Cattell pointed out, with this drug the most susceptible animal of a group requires about a fourth of what the most tolerant requires to produce the same effect, a difference of about 400 per cent. As drugs go, this is a relatively small variation. As an example, consider epinephrine. A half-milligram of epinephrine injected subcutaneously in some persons will cause palpitation and a good deal of nervous disturbance, will it not Dr. Loveless?

DR. LOVELESS: Yes.

DR. GOLD: A few weeks ago I saw a patient in complete heart block with Adams-Stokes attack who was given 10 mg. of epinephrine in ten hours by intramusclar injection to keep his ventricles going. There was not the slightest indication that he was disturbed by the action of epinephrine. Have you any explanation of that, Dr. Loveless?

DR. LOVELESS: They might have picked up a placebo.

DR. GOLD: It was a fresh bottle of epinephrine.

DR. GARB: Are the newer drugs implicated to a large extent in these toxic reactions or is it simply a case of our becoming more aware of the toxic reactions which occur just as frequently with the older drugs?

DR. GOLD: What do you think about that, Dr. Barr?

DR. BARR: In our wards, digitalis preparations were the most frequent cause of toxic reactions. We were responsible for only a small part of these accidents. Most of them had developed before the patient entered the hospital. Our own troubles usually arose when digitalis was used with diuretics and other treatment that disturbed homeostasis.

DR. SEYMOUR RINZLER: For my own future comfort, I wonder if Dr. Barr would tell us whether or not some of these reactions could have been prevented with a more searching history. Take the girl with asthma, for example; if somebody had known about that, could the untoward reaction have been prevented?

DR. BARR: I think we should be especially

careful with people who have a history of hypersensitivity. Reactions, however, are by no means confined to this group and we could not eliminate all risks by even the most searching history.

DR. CATTELL: I would like to add two examples which I came across recently, illustrating the dangers of therapy. One relates to blood transfusions. In this clipping from the *Journal of the American Medical Association* it is stated that even in the best-run institutions it is estimated that the mortality rate from blood transfusions is approximately 1 in 1,000 to 3,000. In view of the fact that approximately 3.5 million transfusions are given annually in this country, the number of deaths would be about 1,700, making this cause of death as frequent as those resulting from appendicitis or anesthesia.

The second is from the New York Times, which I presume is an accurate report. It relates to some work of Dr. Hinton, of the Department of Surgery at the New York University College of Medicine: "In a special series of 212 deaths from the thirty leading medical centers, the researchers determined that one death from cardiac failure had occurred from each of 2,384 anesthetizations."

It may be questioned whether or not the risk is greater than that presented earlier in relation to some of the newer drugs but I think these examples certainly point up the danger of therapy under the special circumstances.

DR. MODELL: From time to time when we get into some difficulty with a drug it is suggested that we make a preliminary test either by giving a small dose first or sometimes a skin test. It is my impression that these preliminary efforts soon are forgotten. Is that because they have no value?

DR. GOLD: I wonder if Dr. Loveless has anything to say about the prospect of getting into trouble with a drug by making some preliminary tests?

DR. LOVELESS: I assume we are concerned with drug reactions such as urticaria, asthma or shock. In those cases drugs such as penicillin give a small proportion of positive skin test reactions to intracutaneous scratch tests even when the person is known to be sensitive. I think it is only a few per cent. I do not think they are worth doing because when the result is negative it gives a false sense of security. It is much more important to get a thorough history before the person is tested with a drug, and if his history indicates that he is probably allergic the decision whether or not to go ahead and make a test is made cautiously. The history is worth much more than any test, and in the case of drugs the test is often dangerous.

VISITOR: In connection with what Dr. Loveless and Dr. Cattell have said, there are two things that come to my mind. One is a recent report in the *Annals of Allergy* describing a systemic reaction with as little as three millionths of a unit of penicillin. The other reference is a survey made by Dr. Glaser in Rochester on 500 children, 360 of whom, I believe, were allergic and 140 or so were non-allergic. Drug reactions in the history of those children were as follows: about 20 per cent in the allergic group and about 2 per cent in the non-allergic group. So I agree with Dr. Loveless that skin tests for drug sensitivity are not very satisfactory and that the case history is an important consideration. Every new drug given to a person with an allergic history should be introduced with great caution.

DR. CATTELL: I would like to ask Dr. de Gara in that connection whether or not the observation of Rich has useful applications. I refer to his work with the sulfonamides in which he found that while he could not get a positive skin test to a sulfonamide to which the patient was sensitive, by combining it with globulin a material was formed to which the skin test did become positive.

DR. PAUL F. DE GARA: I do not think any more has been done about that. In isolated instances it is possible to demonstrate sensitivity by passive transfer. Dr. Whitmore and I had a patient several years ago in whom we were able to demonstrate sensitivity to sulfadiazine by a positive reaction to this procedure. However, this happens only rarely even in patients known to be sensitive to the drug.

DR. GOLD: Dr. Riker.

DR. WALTER F. RIKER, JR.: This is outside my field, but I was wondering with regard to the hyper-responsive people whether or not we are talking about a special category or are recognizing the fact that the population is not really homogeneous. In other words, if we were able to centrifuge these people to their proper layer and then study them, would we not then be able to construct a distribution curve?

DR. CATTELL: You are suggesting that what we speak of as an allergic reaction might represent a degree of sensitivity greater than usual, but an effect which could be elicited from all members of the population?

DR. RIKER: That is right.

DR. GOLD: That the difference between those two labels is not qualitative but quantitative?

DR. CATTELL: One answer to Dr. Riker's point is that, in general, we do not recognize the graded response to dosage in these allergic reactions. An extremely large dose may produce the same effect as a small one. The dangers of the intracutaneous skin test have been emphasized.

DR. LOVELESS: I take issue with that. If one quantitates a patient's reactivity and tests the threshold of response to drugs applied to the skin or eye, or even injected into the blood stream, there is a wide range of susceptibility in an allergic population. Although the dose is small, the range is wide. So there again I am sure the distribution curve is similar, but very far down in the dosage scale.

DR. RIKER: That is exactly my point.

DR. CATTELL: It is a different relationship because an effect is obtained from a fraction of the therapeutic dose, that required to produce a pharmacologic effect. In the case of some drugs such as penicillin even a large dose may not kill the patient. So that certainly there is a discontinuity in dose between the two categories of response.

DR. RIKER: True, I mean to dissociate the two categories, not to relate them.

DR. LOVELESS: The difference in the level of susceptibility between the normal therapeutic range and the allergic range is great. However, if we measure the small doses causing allergic reactions there also is a wide range of effect.

DR. CATTELL: Thank you, I accept your correction.

DR. LOVELESS: I think of an example of a patient who was so allergic to two-tenths of a unit of insulin that a rash developed followed by shock and unconsciousness. That is far from the therapeutic dose but I think we could give her a smaller dose without getting any reaction.

DR. CATTELL: Obviously there must be some dose too small to give a reaction. But here we are dealing with a response which bears no relation to the usual therapeutic action of the drug. It is qualitatively different and is not part of the dose-response curve representing the pharmacologic action of insulin. To make the distinction clearer we might consider the dose of an inert protein which in the normal person has no pharmacologic effect even with large doses but in the sensitized person results in a violent reaction.

DR. GOLD: There comes to my mind the example of an allergic reaction to mercuhydrin® by intramuscular injection. The patient received 2 cc. and a chill, mouth rash, and temperature to 103°F. developed. The injection was repeated several times before someone caught on to the fact that the person was reacting strangely to the drug. I think it was found that he reacted to a tenth and five-hundredths of a cc. of the preparation. This, I think, is an allergic reaction, because most people would not respond that way to any dosage.

VISITOR: I would like to mention a case which illustrates the fact that even a good history is not dependable. After the fourth pregnancy a woman was given pituitrin.® She reacted severely with angioneurotic edema and swelling of the tongue and almost died. Here is a case where pituitrin used in successive pregnancies elicited no untoward reaction and in the fifth pregnancy the patient nearly died. There was no history of allergy in this case.

DR. GOLD: You will not discover all of them.

DR. TRAVELL: I would like to come back to Dr. Riker's question and raise the problem of the variations in the reactions of different people to morphine. In some women the reaction is excitatory rather than narcotic. That is the usual predictable action of morphine in the cat, whereas sedation is the usual effect in the dog. In the human population, in those few people who become almost maniacal with therapeutic doses of morphine, are we dealing with idiosyncrasies or with manifestation of the basic pharmacologic action which is manifested by a small part of the population?

DR. RIKER: Just because all members of the group are of the same species, *homo sapiens*, does not assure biochemical homogeneity.

DR. CATTELL: Because the manifestations correspond to the known pharmacologic actions of morphine, it may safely be assumed that the few cases in which this occurs represent the more susceptible persons encompassed within the normal range of variation.

DR. GOLD: I am afraid our time is up.

SUMMARY

DR. SOLOMON GARB: The importance of individual variation in response to a drug was discussed and illustrated. When an average or mean dose of a drug is administered, a certain percentage of patients will show less than average response, others will show greater than average response, and in some toxicity will develop.

The extent of individual variation is not fully appreciated. In the cat assay of digitalis, one of the best standardized and least variable responses to drugs, the difference in dosage between the most and the least sensitive animals is about 400 per cent. With other drugs the range may be even greater.

Some discussion developed over the separation of predictable toxic reactions based on the usual pharmacologic action of a drug from the allergic type of reaction. The gaps in our understanding of these phenomena were brought out. The possibility was raised that these seemingly dissimilar reactions may result from the fact that the population is not homogeneous.

The clinical importance of toxic reactions to drugs was discussed and it was pointed out that they constitute a leading cause of illness at the present time. Much of the danger comes, not from any particular drug or procedure, but from the multiplicity of therapeutic and diagnostic agents used in misguided attempts at thoroughness. The point was forcefully made that no therapeutic or diagnostic procedure is without risk. Tragic accidents have followed the use of a drug or procedure which the patient did not need in the first place. The physician should consider such risks carefully and refrain from actions not clearly necessary.

Some drugs may cause delayed toxic reactions which are not recognized as drug reactions, since they mimic or may even be identical with diseases previously thought to be non-iatrogenic. There was general agreement that the incidence of serious reactions to therapeutic and diagnostic procedures is alarmingly high and that published figures are probably lower than the actual incidence. This emphasizes the importance of the ancient medical precept: "Above all, do no harm."

Clinico-pathologic Conference

Disproportionate Dyspnea in Recurrent Cardiac Insufficiency

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THIS white housewife, fifty-five years of age, was admitted to the Barnes Hospital for the third time on November 28, 1956. She died on December 7, 1956. Her chief complaint was heart trouble of about twenty years' duration. The patient's first admission to the hospital was from August 1, 1954 to August 17, 1954. During childhood she had frequent sore throats which were often associated with cervical lymphadenopathy, epistaxis and abdominal pain. She vaguely remembered having a bout of rheumatism when she was fourteen or fifteen years old. In 1927, she went through a normal pregnancy without difficulty. However, during her second and last pregnancy in 1932 dyspnea developed on exertion, and she noted orthopnea and swelling of her ankles. At that time she was told that her heart was enlarged. Following delivery her symptoms gradually subsided. At various times thereafter she was told by physicians that she had rheumatic heart disease. In 1953, a physician prescribed a regimen of digitalis for auricular fibrillation. She then did well until five months before her first admission when right-sided pleuritic pain, hemoptysis and fever with a temperature of an unknown degree developed. She was hospitalized for seven weeks in an osteopathic hospital with the diagnosis of pneumonia. She was told that she did not tolerate digitalis. On therapy with antibiotics and bed rest she lost 20 pounds. Following discharge her course was progressively downhill with increasing dyspnea on exertion, orthopnea and bouts of nocturnal dyspnea. She was also bothered by persistent soreness in the lower right side of the chest and in the upper right side of the abdomen. She had been confined to bed for the two weeks preceding this admission.

The patient's mother had died at the age of thirty of an unknown type of heart disease. Otherwise, the family history was non-contributory. Aside from the present illness, the patient had no complaints.

Physical examination revealed the following: The temperature was 37°C.; pulse, 128; respirations, 28; blood pressure, 120/80 mm. Hg. The patient appeared chronically ill and moderately dyspneic. There was no cyanosis. The eyes, ears, nose and throat were normal without evidence of infection. The teeth were carious. There was no lymphadenopathy and the thyroid was not enlarged. There was a slight increase in the anteroposterior diameter of the chest. There was impaired motion of the lower right side of the chest and the right side of the diaphragm. Rales were heard at both lung bases. The cardiac rhythm was totally irregular. The point of maximal impulse was diffuse in the 5th and 6th intercostal space in the anterior axillary line. The pulmonic second sound was accentuated. There was a loud, rough, systolic murmur in the apex which was transmitted to the axilla and a second rough, systolic murmur was heard at the aortic area. After the cardiac rate had slowed, three separate diastolic murmurs were heard, at the aortic and tricuspid areas and at the apex. The liver was firm and descended 4 finger-breadths below the right costal margin. It did not pulsate. There was no peripheral edema. Two observers suggested clubbing of the fingers.

Laboratory data revealed the following: The hemoglobin was 12.6 gm./100 ml. The white blood cell count was 4,050 per cu. mm. with the following differential: eosinophils, 1 per cent; polymorphonuclear leucocytes, 81 per cent; lymphocytes, 17 per cent; monocytes 1 per cent.

The urine specific gravity was 1.005 and the pH was 7.5; there was no albumin or sugar; a rare red blood cell, 8 to 10 white blood cells, and an occasional finely granular cast were seen in the centrifuged urine sediment. The cardiolipin reaction was negative. Blood chemical determinations were as follows: non-protein nitrogen, 15 mg./100 ml.; fasting blood sugar, 76 mg./100 ml.; cephalin cholesterol flocculation test, 3 plus; thymol turbidity, 19.3 units; direct acting bilirubin, 1.6 mg./100 ml.; total bilirubin, 1.6 mg./100 ml.; alkaline phosphatase, 3.3 Bodansky units; total serum protein, 7.5 gm./100 ml., with albumin 3.9 and globulin 3.6; sodium, 144 mEq./L.; potassium, 3.4 mEq./L.; carbon dioxide, 22.5 mEq./L.; chloride, 108 mEq./L. The prothrombin concentration was 36 per cent of normal. The antistreptolysin 0 titer was greater than 500 units. The packed cell volume was 44 per cent and the actual sedimentation index 31 mm. per hour. The electrocardiogram was read as follows: "Auricular flutter with variable block occasionally passing into transient auricular fibrillation. Small notched "r" waves in V_1 and V_3 R with marked clockwise rotation suggestive but not diagnostic of right ventricular enlargement." Frequent ventricular premature contractions and digitalis effect were noted. Roentgenographic examination of the chest was interpreted as showing marked cardiac enlargement with left auricular enlargement and a right pleural effusion. Culture of the throat grew neisseria, alpha streptococcus, and Micrococcus albus. Venous pressure was 90 mm. of saline rising to 120 mm. with pressure over the liver. Arm to tongue circulation time was 20 seconds with decholin.®

The patient was maintained on modified bed rest. She received digitalis and was fed on a low salt diet. Her weight dropped 10 pounds with associated clinical improvement. Roentgenographic examination revealed a decrease in the cardiac size and in the right pleural effusion. On the third hospital day, red blood cells appeared in the urine. On the eleventh hospital day, gross hematuria developed associated with frequency and burning. Culture of the urine grew sixteen colonies of non-hemolytic M. albus and a few colonies of coliform bacilli. Penicillin, streptomycin, and later mandelamine® were administered. Findings at cystoscopy on the fourteenth hospital day were interpreted as subsiding hemorrhagic cystitis. At the time of discharge from the hospital, the cephalin cholesterol flocculation test was negative and the thymol turbidity was 7.0 units.

The patient was admitted for the second time on September 21, 1954. She was discharged on October 1, 1954. The patient had felt quite well on very limited activity, low salt diet, and maintenance digitalis. Three weeks before this admission her private physician had found pus cells in her urine. Because of this finding she had been given pills. She entered the hospital for extraction of her remaining carious teeth.

Physical examination revealed the following: The temperature was 37°c.; pulse, 90; respiration, 18; blood pressure, 170/75 mm. Hg. The patient was in no distress. The lungs were clear. A precordial heave was noted. The point of maximal impulse was 8 to 9 cm. from the midsternal line in the 5th and 6th intercostal space. Apical murmurs were described as well as a grade 2, harsh systolic murmur and a grade 2, soft mid-diastolic murmur at the aortic area. Resistance was felt 4 cm. below the right costal margin, but the liver edge was not palpable. The remainder of the physical examination was unchanged from the preceding admission.

Laboratory data revealed that the blood counts taken on admission and urinalysis were not significantly changed from those of the previous admission. No pus cells were seen in the urine. Blood chemical determinations included: total serum protein, 8.2 gm./100 ml.; with albumin, 4.1 and globulin, 4.1. Cephalin-cholesterol flocculation was $+-$, thymol turbidity, 10.5 units; total bilirubin was less than 0.8 mg./100 ml. The antistreptolysin 0 titer was 400 units. Culture of the throat did not grow any beta hemolytic streptococci. Electrocardiogram showed no essential change.

The patient's general condition remained unchanged. Intramuscular penicillin was administered prophylactically throughout her hospital stay. Her remaining teeth were extracted under local anesthesia without difficulty. The highest recorded blood pressure during this admission was 170/100 mm. Hg.

The patient was admitted to the hospital for the third time on November 28, 1956. She was discharged on December 7, 1956. Following the preceding admission, the patient had continued to take digitalis and to restrict her salt intake. She had been taking serpasil® for mild blood pressure elevation. Her activities had been considerably restricted; she did little walking and did not go up or down stairs. She had slight

shortness of breath and slept on one or two pillows. There was no nocturnal dyspnea or peripheral edema. She had a slight hacking cough. Four weeks before admission the patient noticed weakness associated with loss of appetite. Dyspnea increased considerably but there was little coughing and no known fever. For one or two weeks before admission she had noted an aching in the right flank and right upper quadrant coming on with getting up and not increased by respiration.

On physical examination her temperature was 36°C., pulse, 100 (apical) 82 (radial); respirations, 22; blood pressure, 110/60 mm. Hg. The patient did not appear acutely ill. One observer believed she was slightly cyanotic. A few petechiae were seen over the shoulder region. The eyes were normal. Fundi were normal. There was no evidence of infection in the ears, nose or throat. There was cervical erosion at os cervici without bleeding. The chest was clear to percussion. Rales were present in both lung bases. Aortic systolic and diastolic murmurs and an apical systolic murmur were present. No apical diastolic murmur was heard. The liver was palpable 5 to 6 cm. below the right costal margin. The remainder of the physical examination was essentially the same as before.

Laboratory data revealed the following: Hemoglobin was 15.9 gm./100 ml., and the white blood count was 9,650 per cu. mm. with the following differential: basophils, 1 per cent; polymorphonuclear leucocytes, 74 per cent; lymphocytes, 21 per cent; monocytes, 4 per cent. The red blood cells and platelets appeared normal on stained film of the blood. Urine specific gravity was 1.012 and the pH was 4.5; there was 2 plus albuminuria and no glycosuria; microscopic examination on the centrifuged sediment disclosed occasional white blood cells and occasional epithelial cells. Blood chemical determinations were as follows: non-protein nitrogen, 30 mg./100 ml.; fasting blood sugar, 104 mg./100 ml.; total bilirubin, 1.8 mg./100 ml. with direct reacting bilirubin, 0.2 mg. 100 ml. and indirect reacting bilirubin, 1.6 mg./100 ml.; alkaline phosphatase, 6.6 Bodansky units; total serum protein, 8.5 gm./100 ml., with albumin, 4.5 gm./100 ml., and globulin, 4.0 gm./100 ml.; cephalin cholesterol flocculation, 2 plus; thymol turbidity, 7.3 units. The antistreptolysin 0 titer was 316 units and the C-reactive protein was 2 plus. The packed cell volume was 55 per cent and the actual sedimentation index 0 mm. per hour. Electrocardiogram was interpreted as follows: "although the record shows the conventional pattern of incomplete right bundle branch block, it probably represents right ventricular enlargement which can produce this same pattern." Auricular fibrillation was also noted on the tracing. Venous pressure was 240 mm. of saline. Arm to tongue circulation time was 60 seconds.

The patient was maintained on bed rest. She was given a 500 mg. salt diet and phenobarbital for sedation. The usual maintenance dose of digitalis was doubled to 0.2 gm. per day in the hope of getting more therapeutic effect. Her cardiac rate continued to be fairly rapid with considerable variation. It was frequently between 110 to 120, but on the fifth hospital day it was recorded as high as 160. She complained of feeling weak and miserable. She seemed anxious and depressed. The basilar rales persisted. Respiration was frequently labored. Blood pressure varied between 90/70 and 130/70 mm. Hg. She had no fever and no peripheral edema. Subacute bacterial endocarditis was considered as a possible cause of her downhill course. Three blood cultures obtained on the fourth and fifth hospital days were negative at the time of death. One repeat urinalysis disclosed no red blood cells and a trace of albumin. Another disclosed only a rare red blood cell and 2 plus albuminuria. On the sixth hospital day the serum electrolytes were: sodium, 128.6 mEq./L.; potassium, 5.3 mEq./L.; carbon dioxide, 18.1 mEq./L.; chloride, 95 mEq./L. The non-protein nitrogen was 36 mg./100 ml. By the next day the non-protein nitrogen had reached 49 mEq./L. and the sodium had fallen to 123.6 mEq./L. On the ninth hospital day the patient complained of epigastric pain and stated that she had felt similar pain off and on for three years. She was given gelusil® and probanthine.® Early on the tenth hospital day her course seemed to go rapidly downhill. Her respiration became more rapid and labored. Cyanosis was marked. Her blood pressure was unobtainable. Her heart rate remained slow, approximately 60. She became extremely cyanotic and died several hours later.

CLINICAL DISCUSSION

DR. JOHN R. SMITH: In 1932, this woman, during her second pregnancy, was told that she had cardiac enlargement. Thereafter she was reminded at various times by physicians that she had rheumatic heart disease. Not until three

years before her death did she begin to have significant difficulty. To those who observed this patient over a long period of time, there seemed to be justification for the diagnoses of rheumatic heart disease. In order to complete the clinical picture, I shall ask Dr. Humphrey to comment on the roentgenograms of the chest.

DR. HARVEY A. HUMPHREY: The first and last time that we saw this patient was two years and four months before death. Two examinations of the chest were performed. The first on August 2, 1954, showed enlargement of the heart. There was a collection of fluid in the right pleural space. Triangular zones of increased density were present in the lower half of the right lung, predominantly in the right middle and lower lobes. The pulmonary vessels within the lungs appeared slightly enlarged and somewhat indistinct in outline. The aorta was elongated and prominent for a person this age. The left bronchus appeared elevated and abnormally horizontal in its course. This would suggest, in addition to the ventricular enlargement, left auricular enlargement. There was a calcified primary complex in the left lung. On the oblique projection some displacement posteriorly of the barium-filled esophagus could be noted. There was right ventricle enlargement as well as left ventricular enlargement. There was also a density in the apex of the right lower lobe, which could be interpreted as pulmonary infarction. The lateral projection indicated the abnormally increased A-P diameter of the heart and specifically the posterior displacement of the barium-filled esophagus. On the next examination, nine days later, the heart remained essentially the same, in size and shape, but there was a decrease in the amount of pleural fluid and thickening and some resolution of the previously noted density in the right lower and middle lobes. The elongated aorta was again noted. The left lung was essentially clear. I believe that at that time there was reasonably good x-ray evidence of cardiac enlargement, moderately pronounced, left ventricular enlargement, right ventricular enlargement, lesser degrees of left auricular and right auricular enlargement. We suspect that there was aortic valve disease with predominantly aortic insufficiency; mitral valve insufficiency and a question of tricuspic insufficiency because of the enlargement of the right auricle and ventricle. Pulmonary vascular congestion probably associated with some pulmonary hypertension appeared probable inasmuch as the vessels appeared dilated. Pulmonary emboli, pulmonary infarcts in the right lower and middle lobes and a right pleural effusion were also present.

DR. SMITH: Thank you Dr. Humphrey. During the later years of her life, a number of disorders of rhythm, and eventually auricular fibrillation developed. I shall ask Dr. Andresen to review the essential features of the electrocardiograms, and to comment on the arrhythmias which were noted.

DR. DONALD C. ANDRESEN: There were two electrocardiograms available for interpretation. The first was taken in August, 1954, during the patient's first admission and the last in December, 1956, during her third admission. On the first tracing the following abnormalities were noted: atrial flutter was present and was best demonstrated in V1 in which the symmetrical regular flutter waves were easily seen with irregularly interspersed ventricular complexes. An RR′ in V1 and V3R, plus moderate clockwise rotation and a prominent R in AVR was also present. These changes were suggestive either of an incomplete right bundle branch block or possibly right ventricular enlargement, but their inconclusive nature made it difficult to state specifically which of these two was the most likely. Frequent ventricular premature contractions and digitalis effect were also present. On the second tracing, atrial flutter was replaced by atrial fibrillation. This was again best seen in V1 in which the regular symmetric flutter waves were absent and were supplanted by small irregular waves of varying magnitude and duration. The changes previously noted in regards to right ventricular enlargement or incomplete right bundle branch block were more pronounced. She had right axis deviation, as shown by the small R wave in standard lead I and the very prominent R wave in standard lead III. There was also a more prominent R wave in AVR as well as in V1 and V3R. Similarly the clockwise rotation was again much more evident as shown by a deep S wave in V6. This record I think was more compatible with the diagnosis of right ventricle enlargement, and the diagnosis of incomplete right bundle branch block appeared less likely. There was no evidence of left ventricular enlargement. In summary, then, the first tracing showed atrial flutter with varying AV block, questionable incomplete right bundle branch block or right ventricle enlargement, digitalis effect and ventricular

premature contractions. The second electrocardiogram demonstrated atrial fibrillation and was more suggestive of right ventricular enlargement. Digitalis effect was still present.

DR. SMITH: Now, there are several ways in which this case may be analyzed. It might be well to return to the beginning of this patient's disease. This probably occured when she was young and had one or more attacks of rheumatic fever. Since knowledge of streptococcal organisms is extremely important with respect to the prevention of this disease, I shall ask Dr. William Perry to comment on beta hemolytic streptococci, their ubiquity, so to speak, and how people may become infected by these organisms.

DR. WILLIAM D. PERRY: In general, it may be said that clinical recognition of a beta hemolytic streptococcus infection often presents a great deal of difficulty. The picture can vary from the typical sore throat associated with inflammatory exudate, high fever and bilateral lymph node enlargement to a minor respiratory infection which cannot be distinguished from a cold. Many of you are aware that during epidemic times, in a double blind study, the diagnosis can be made only approximately 70 per cent of the time. As far as the spread of the streptococcus is concerned, as nearly as can be ascertained this must be from man to man and not from floor or bedclothing or other fomites to man. The agent currently recommended for the treatment of this infection is penicillin rather than any other agent. An effective form of penicillin therapy appears to be the injection of one dose of 1,200,000 units of bicillin.® The use of sulfonamide in treating streptococcus pharyngitis is not recommended because the incidence of rheumatic fever following the streptococcal infection is not prevented by this drug. On the other hand, with the eradication of the organism, by use of an antibiotic such as penicillin, the incidence of rheumatic fever is significantly decreased.

DR. SMITH: This patient did not have the benefit of such measures; therefore, the rheumatic fever presumably ran its course. It smouldered and produced chronic valvular heart disease. Those who observed this patient agreed that she had mitral stenosis, mitral insufficiency and aortic insufficiency. A harsh aortic systolic murmur was heard at times. However, this murmur was not accompanied by a thrill and the aortic second sound was not specifically described in the chart. You recall that the diagnosis of classic aortic stenosis can be made when there is a harsh aortic systolic murmur, accompanied by a systolic thrill and a diminished or absent aortic second sound. Some of those signs were lacking in this case. Dr. Parker, what are your ideas regarding the possibility of aortic stenosis here? When do you think this diagnosis is tenable in the absence of the "classical" physical signs?

DR. BRENT M. PARKER: One should think of the diagnosis of aortic stenosis whenever there is a significant systolic murmur at the aortic area. In recent years Kumpe and Bean* and White† have both emphasized that the usual accompaniments of the lesion such as a diminished aortic second sound, plateau pulse, narrow pulse pressure and a systolic thrill at the aortic area may be entirely absent in cases which are proved at autopsy to be aortic stenosis. The only finding present, therefore, may be a loud systolic murmur at the aortic area. Thus, in this case, with this apparently significant murmur heard in the aortic area, I believe that aortic stenosis should be considered. It is worth noting that a second sound may be heard at the aortic area in some instances because of transmission of a loud pulmonic second sound.

DR. SMITH: In other words, this patient probably had a developing, or partially developed, aortic stenosis. This patient also displayed a mitral systolic murmur which was rough and loud. The diastolic murmur, heard at the apex, was not nearly so conspicuous. Nevertheless, the diagnosis of mitral stenosis seemed to be justified. Dr. Diettert, will you sketch for us briefly the physiologic consequences of mitral stenosis, with particular reference to the pulmonary vascular system? This may be of importance as we go on with our deliberation.

DR. GERALD DIETTERT: It has been shown in animal experiments that narrowing of the mitral orifice produces a temporary decrease in the left ventricular inflow and stroke output, but this is quickly compensated for by an increased diastolic volume and pressure in the left atrium. Further, in late diastole the increased diastolic volume leads to a more forceful atrial contraction and a greater discharge of blood. Similar effects occur in mitral stenosis. The ability of the left atrium to compensate completely is limited because of a relatively weak muscular chamber frequently in-

* KUMPE, C. W. and BEAN, W. B. Aortic stenosis: a study of the clinical and pathologic aspects of 107 proved cases. *Medicine*, 27: 139, 1948.

† WHITE, P. D. Heart Disease, 4th Ed., P. 689. New York, 1951. Macmillan.

volved by rheumatic fever and because of the frequent presence of auricular fibrillation. Because of the absence of valves between the left atrium and the pulmonary vein, the increased left auricular pressure is transmitted via the pul-.nonary veins to the pulmonary capillary bed, resulting in pulmonary congestion. Many clinical features of mitral stenosis are the result of the increased pulmonary blood volume and engorgement of the lungs. Among the resulting physiologic disturbances are loss of elasticity, reduction in the vital capacity of the lungs, slowing of the pulmonary circulation and the finding of increased "capillary" wedge pressures on the right heart catheterization. Since the pulmonary artery pressure is related to the right ventricular stroke output, pulmonary vascular resistance and the left atrial pressure, it can be seen that a change in any one of these factors will be followed by an alteration in one or more of the other components. There is evidence to suggest that the rise in the left atrial pressure is initially followed by a fall in pulmonary vascular resistance. Thus, right ventricular output and pulmonary pressure are maintained. However, once the capacity of the pulmonary vascular bed to compensate is exceeded, pulmonary hypertension and right ventricular hypertrophy develop.

DR. SMITH: Dr. Diettert, is it true in some instances, that in patients with advanced mitral stenosis, pulmonary arterial pressures by catheterization may be so increased as to approach systemic arterial pressures in magnitude?

DR. DIETTERT: That is certainly true.

DR. SMITH: In patients with mitral stenosis extreme degrees of pulmonary arteriosclerosis may also develop. This may be on the basis of small emboli or other intrinsic changes in the vessels. Pulmonary atherosclerosis was a diagnosis entertained by her attending physicians. At no time was the diagnosis of congenital malformation of the heart ever entered upon, at least not seriously. Dr. Bercu, is there anything at all in the information at hand that would lead you to believe there is a congenital cardiac defect present?

DR. BERNARD BERCU: I do not think so Dr. Smith. The evidence for mitral stenosis and aortic valve disease is so certain and the x-ray picture so confirmatory for this diagnosis that I think, with the evidence at hand, one would not be able to make a case for congenital heart disease.

DR. SMITH: During the patient's course in the hospital, congestive heart failure of varying severity developed. Failure came and went; cleared, and got worse again. She was observed on each hospital admission to have hepatic enlargement, and a good deal was made of this finding. Dr. Shank, do you think that the liver function studies are compatible with prolonged congestion, or is there any reason to believe that some other form of liver disease was present?

DR. ROBERT E. SHANK: The findings listed are wholly compatible with hepatic dysfunction associated with chronic passive congestion. Since the disease had persisted so long, I think there would be fibrotic changes with central type of fibrosis. On the other hand, I believe one should be aware that in long maintained cardiac decompensation, there are general nutritional disturbances. The metabolic rate is increased, while the appetite is decreased, allowing for the development of nutritional defects. It is for this reason, that not uncommonly in long standing chronic passive congestion of the liver, one also finds the changes of portal cirrhosis. This patient did not have the manifestations of portal hypertension.

DR. SMITH: Is the serum globulin level somewhat higher than is ordinarily observed in congestive disease of the liver? It seems to me it is.

DR. SHANK: This might afford reason for suspecting another process in this liver. However, the highest globulin value recorded was 4.2 gm. per cent, a level which might have occurred because of hemoconcentration. The bilirubin values are also of interest. The elevation recorded may result from a number of courses in chronic cardiac decompensation. One is anoxia of the liver interfering with the handling of these pigments so that they accumulate in the blood stream. In addition, embolic phenomena may occur, particularly in the lung with subsequent hemolysis causing elevation in bilirubin values. Again, in the greatly swollen liver there may actually be compression of small bile ducts so that there is retention on that basis. Any one, or all, of the mechanisms listed may have produced the relatively small retention of bilirubin demonstrated in this patient.

DR. SMITH: It seems to me also that congestion was the most likely cause for the deviations in liver function. Now, as time went on, and particularly during her second admission, Dr. Massie, this patient was observed with a blood pressure of 170/100 mm. Hg. For this reason she was given small doses of serpasil or some other

tranquillizing drug. Will you comment upon the mechanism of this elevation of blood pressure? Do you think it was on the basis of cardiac failure, or do you think that there was some other mechanism?

DR. EDWARD MASSIE: I would hesitate to incriminate the heart *per se* as the basis of the elevated blood pressure reading. Actually, in large series of cases studied of patients who had blood pressure elevations before heart failure, or after prolonged heart failure, the blood pressure did not change significantly. I should think one would have to find another etiologic factor, and this factor could be in the kidneys, judging from description of the course of events.

DR. SMITH: What do you think this course of events was?

DR. MASSIE: Well, I noted that on the first admission, she had hematuria. I suspected that the patient might have had renal emboli as a result of which certain glomerular changes might have occurred, to produce a renal factor in her hypertension. In other words, primary renal disease with secondary hypertension.

DR. SMITH: Do you think there was an element of pyelonephritis?

DR. MASSIE: Renal infarction seems most likely, but pyelonephritis certainly could have been present.

DR. SMITH: Dr. Bricker, what is your opinion regarding the renal status?

DR. NEAL BRICKER: I believe the majority of findings including the eventual development of azotemia and hyponatremia, are explicable within the framework of rheumatic heart disease and congestive heart failure. On the other hand, it is difficult to exclude independent or associated organic renal disease. In view of the clinical diagnosis of subacute bacterial endocarditis, we might look for evidence of focal embolic or acute diffuse glomerulonephritis. However, the urine sediment examinations listed in the protocol do not support either diagnosis. The one episode of gross hematuria seems adequately explained by the cystoscopic finding of hemorrhagic cystitis. Several other possibilities may be mentioned. It is quite possible that a patient with tight mitral stenosis, atrial fibrillation, and thrombus in the left atrium, may shower small emboli to the kidneys. In addition the age group in which she fell would predispose her to the development of arteriolar nephrosclerosis. Finally, the possibility exists that she had progressive pyelonephritis. However, we have very little positive evidence to favor the latter diagnosis. Perhaps the most valuable laboratory finding in support of the diagnosis of active pyelonephritis is bacilluria, and this is not mentioned in the protocol. The albuminuria may be explained on the basis of heart failure, and the examinations of the urine sediment in this hospital generally showed very few if any white cells. Pus cells were noted in the urine in an examination performed by another physician but the number of these is not mentioned.

DR. HERBERT ZIMMERMAN: I would like to point out one other physiologic explanation for this hypertension. It is well known that people who go into acute decompensation may frequently present with a hypertension, which then disappears when the patient is compensated. In 1953, the group in London demonstrated that there was a baroreceptor in the carotid sinus. They demonstrated that an increased cardiac output resulted in peripheral vasodilatation. Decreased cardiac output was associated with peripheral vasoconstriction. We are dealing here with a patient who had a lesion which would give her a decreased cardiac output. I think when patients arrive at a critical point of decreased cardiac output, these baroreceptors may come into play and cause vasoconstriction and consequent hypertension.

DR. SMITH: It would be interesting to have your thoughts on the following questions. If this vasoconstriction occurs on the arteriolar side of the circulation to produce hypertension, do you think that the venules of the peripheral circulatory system likewise constrict? Is it possible that in consequence of the latter, the venous pressure rises under these circumstances?

DR. HERBERT ZIMMERMAN: Yes. It seems probable that there are pressure receptors throughout the entire vascular tree on the venous side and also in the pulmonary vascular tree. At the present time one can only speculate.

DR. SMITH: During her last admission to this hospital, this patient's condition declined very rapidly. There were petechiae over the shoulders and marked dyspnea and discomfort. She felt worn out and weak, and there was every reason to believe that she was indeed in serious difficulty. It has been the custom in the past to fall back upon the contention that, when patients with rheumatic heart disease decline rapidly, one of the underlying difficulties is reactivated acute myocarditis. Dr. Massie, will you comment

on this possibility? When do you make the diagnosis of a recrudescence of myocarditis?

DR. MASSIE: At this patient's age, I would be hesitant to think of reactivation of rheumatic fever. If there were no symptoms, apart from the heart, I also would not consider this diagnosis strongly.

DR. SMITH: I have thought many times that patients much younger than this, dying with rheumatic heart disease, may have acute myocarditis. However, there was usually no evidence of it at autopsy. Naturally with this patient's decline, there was a good deal of concern on the part of her doctors as to whether or not she had subacute bacterial endocarditis. Blood cultures were obtained which up to the time of her death had grown no organisms. You mentioned this previously, Dr. Bricker. Would you entertain seriously the diagnosis of subacute bacterial endocarditis or do you think that her terminal illness was due to something else?

DR. BRICKER: There are scattered observations which certainly make us consider this diagnosis. Included among these are, the presence of petechiae, the progressively downhill course, and the note that two observers thought she had clubbed fingers. Moreover, we could view the development of hematuria in a different light than that which we discussed previously. However, viewing the situation *in toto*, I personally would think that we do not have enough evidence to support this diagnosis.

DR. SMITH: That leaves us with the question "Why did she die?" Those who saw her were extremely impressed with the degree of dyspnea and cyanosis that developed as her life ebbed. The question is raised as to whether her death occurred from myocardial insufficiency or whether some other event was taking place. Dr. Parker, what do you think of the events?

DR. PARKER: I think it is very likely that she died with multiple pulmonary emboli and with a massive pulmonary embolus as the terminal event. Patients with congestive heart failure who are bedfast are especially apt to have this complication. Also we have evidence that she had a pulmonary infarction in 1954, and pulmonary emboli have a tendency to be recurrent. At the time of her death, she had marked cyanosis, hypotension and increased dyspnea, all of which are frequently seen in massive pulmonary embolization. Finally, her relatively rapid death is in keeping with this diagnosis.

DR. SMITH: May I provoke further discussion from you and ask if you think that there may have been pulmonary arteriosclerosis upon which may have been superimposed spontaneous thrombosis? This is a subtle and very insidious process.

DR. PARKER: I believe that is a very difficult diagnosis to make. The clinical manifestations are sometimes hard to separate from those of pulmonary embolism. The rapid downhill course during her last days is probably against this diagnosis, as most patients with this rare condition usually survive for weeks or months.*

DR. SMITH: Dr. Zimmerman, if this patient were showering small or moderately small pulmonary emboli into the lungs, what would be the effect on the heart and on the pulmonary circulation particularly if superimposed upon the mitral stenosis?

DR. ZIMMERMAN: As has been previously mentioned, the pulmonary artery pressure is dependent upon several factors such as the pulmonary vascular resistance, the gradient of pressure across the pulmonary vascular bed, and the pulmonary output. As showers of emboli reach the pulmonary vascular tree, the cross-sectional area of that pulmonary vascular bed is decreased. The pulmonary vascular bed then attempts to compensate for this, by vasodilatation. When the pulmonary vascular bed becomes almost fixed, the pulmonary artery pressure may go up markedly putting a tremendous strain on the right ventricle causing the right ventricle to fail more than it had previously.

DR. SMITH: Yes. Then as the right ventricle fails, there is pressure peripherally to drive blood to the right ventricle, causing marked dilatation and congestion of the entire venous system and accentuating any degree of cyanosis that might have existed before.

DR. ZIMMERMAN: May I add one thing Dr. Smith? Recently there has been a great deal of interest in the major pulmonary artery thrombosis as mentioned by Dr. Parker. It has been found that in such persons not infrequently thrombosis develops of a major pulmonary artery, usually the right, although it has been found in both. When this occurs, a clinical syndrome develops which is characterized by dyspnea out of proportion to the disease that the patient has and frequently cyanosis. One wonders in this case about such a terminal episode.

DR. SMITH: I think we can address the follow-

* MAGIDSON, O. and JACOBSON, G. Thrombosis of the main pulmonary arteries. *Brit. Heart J.*, 17: 207, 1955.

ing conclusions based on our clinical analysis to the department of pathology. This woman had rheumatic fever at an early age and rheumatic heart disease developed, probably with mitral stenosis and insufficiency and with aortic insufficiency and possibly with aortic stenosis. There will be visible in this heart a rather marked hypertrophy of the right and the left ventricles. The question of subacute bacterial endocarditis cannot be entirely eliminated but we think it is unlikely here. You will find in the lungs perhaps, one or many pulmonary thromboses either of embolic origin or of local origin. I think that is about the best we are going to be able to do.

DR. MASSIE: You did not mention tricuspid valve disease and I thought before closing that, in a patient who has aortic and mitral valve disease associated with a large liver, we should think of tricuspid disease. A murmur is described over that area, and while I think this is not likely, I would not be at all surprised to find tricuspid valve disease also.

DR. SMITH: I am glad you brought that up. I visualized a functional tricuspid insufficiency. Dr. Sherry?

DR. SOL SHERRY: In view of the disproportionate dyspnea and cyanosis, I believe we should consider the possibility of a ball-valve thrombus in the left auricle. In the clinical situation described here, the dyspnea and cyanosis were severe and out of proportion to the other findings. One has to think of other causes for obstruction to pulmonary blood flow; the major discussion has already covered circulatory obstruction through the lungs themselves. Furthermore, in rheumatic heart disease there is the proper setting for large left auricular thrombi to form.

DR. SMITH: That is a very good suggestion. Ball-valve occlusion of a narrowed mitral orifice is one of the less frequent causes of circulatory obstruction, but this circumstance could have been present in our case.

PATHOLOGIC DISCUSSION

DR. DORIS REIMANN: At autopsy this was the body of a fifty-five year old white woman who was of normal development but slight stature. The only external abnormality observed was slight pitting ankle edema. The lungs were heavy and very congested. Neither pulmonary edema nor pulmonary emboli were found. Extensive adhesions covered the entire right lung. Fluid in the right pleural cavity measured about 200 cc. and in the left there were 450 cc. As previously seen radiographically, there was a calcified nodule on the left lower lobe and a calcified lymph node draining this area. In the branches of the pulmonary artery, several sclerotic plaques were found. Cultures of the heart's blood were negative. The heart weighed 510 gm., which is about twice the normal weight for a woman of this size. There were 100 cc. of pericardial fluid and the epicardial surface appeared smooth. The tricuspic and pulmonary valves were normal. The foramen ovale was patent but guarded. The left atrium was bulging and distended. When opened, a large, firm thrombus measuring about 5 cm. across occupied the left auricle. (Fig. 1.) It was attached to a plaque on the anterior wall about 2 cm. in diameter; lines of Zahn indicated antemortem origin. The mitral valve was stenotic, with calcifications and concretions on its edge. The base and the chordae tendinae were also calcified. This valve measured 55 mm. in circumference, about one-half the normal dimension. There was slight thickening of the free edges of the aortic valve, fusion of its commissures and calcification at the bases of its cusps. Slight arteriosclerosis was present in the aorta. The right ventricular wall measured 11 mm., more than twice normal thickness. The left ventricle measured 15 mm., only slightly thicker than normal. The liver gave evidence of extreme chronic passive congestion. The spleen weighed 210 gm., (about twice normal) and was fibrotic and congested. All the lymph nodes of the abdomen and thorax were large and soft, indicating some edema. The duodenal mucosa was also edematous. The left kidney was smaller than the right, which was normal in size. On the surface of the left kidney large flat scars suggested chronic pyelonephritis.

DR. NADYA KONIKOV: The thrombus was composed of blood elements which were laminated into lines of Zahn indicating its antemortem origin. At its attachment to the anterior atrial wall, invasion by fibroblasts from the endocardium could be seen. (Fig. 2.) Beneath the thrombus and elsewhere the endocardium was thickened. The endocardium underlying the thrombus was swollen, probably secondary to the thrombus itself, and in this region the myocardium was also degenerated with interstitial infiltration by inflammatory cells. This infiltration is also probably secondary to the presence of the thrombus. In the auricular appendage a more advanced organization of the thrombus

FIG. 1. The large laminated thrombus filled the left atrium and extended into the left auricular appendage. The atrium has been opened through its posterior wall.

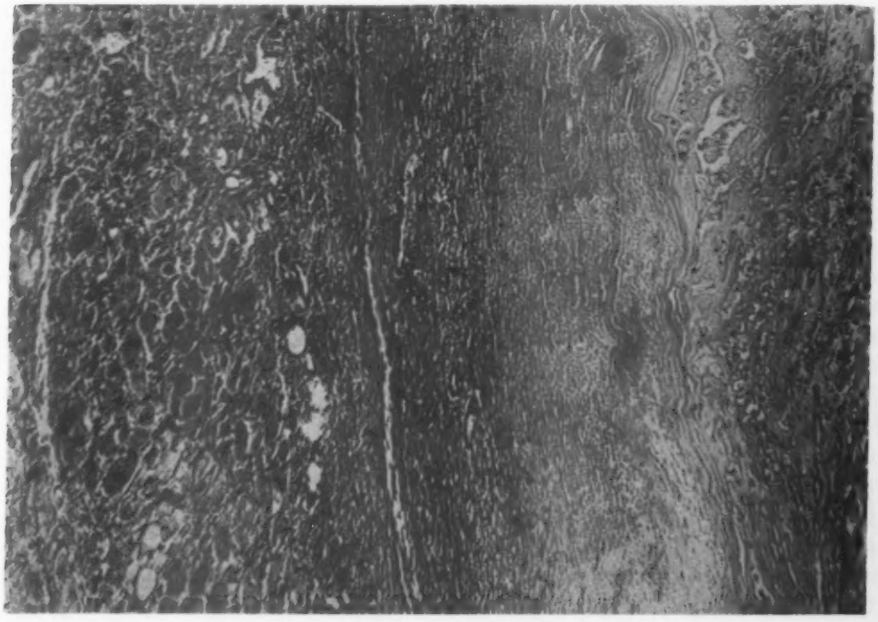

FIG. 2. At the point of attachment of the thrombus on the anterior atrial wall, organization is evidenced by ingrowth of vessels and fibroblasts from the surface of the endocardium. Beneath the thrombus the endocardium is thickened and swollen. The myocardium partly degenerated with granularity and falling out of individual fibers. There is slight interstitial round cell infiltration of the myocardium in this area. Hematoxylin and eosin stain photographed through Wratten B and G filters, × 54.

with ingrowth of fibroblasts and small vessels was present.

The valves were extremely thickened by hyaline collagen and calcium deposits. There was no evidence of rheumatic activity nor of acute bacterial endocarditis.

The lungs were free of infarcts. There were no thrombi in the small vessels and vascular thick-

ening was not prominent. An apparent thickening of the alveolar walls was due in large part to the presence of large dilated capillaries throughout. This is quite commonly seen in patients with mitral stenosis. Any fibrosis present was focal, as is characteristic of lungs of patients with mitral stenosis [*1*].

Other findings included those of marked congestion of the liver and spleen, with centrolobular necrosis of the liver and generalized edema. Focal scars in the kidneys indicated chronic pyelonephritis. The renal vessels were normal.

Final anatomic diagnosis: Stenosis of the mitral valve with calcification of the mitral ring, valve leaflets and chordae tendiniae (history of rheumatic heart disease since childhood); large thrombus (5 cm. in diameter) filling left atrium and left auricle, attached to the anterior wall of left atrium; adhesions of the commissures and fibrous thickening of the aortic valve, with calcification of the bases of the cusps; hypertrophy and dilatation of the right ventricle (heart weighed 510 gm.); pericardial effusion, (100 ml.); acute and chronic congestion of all lobes of lungs; pleural effusion (200 ml. on right, 400 ml. on left); chronic passive congestion of the spleen and liver, severe, with centrolobular necrosis of liver; generalized edema, slight; arteriosclerosis of aorta and pulmonary arteries, moderate; patent foramen ovale, guarded, focal chronic pyelonephritis.

This patient falls into the group of those with rheumatic heart disease with the setting for development of atrial thrombi; patients over the age of forty with mitral stenosis and long standing auricular fibrillation [*2*].

The paucity of significant findings related to the presence of the large thrombus in the left atrium is usual in these cases and accounts for the rarity with which the diagnosis is made antemortem [*3*]. By comparison of the clinical courses of those with mitral stenosis and ball thrombi and those with mitral stenosis alone it is possible to conclude that the degree of dyspnea, cyanosis and cardiac failure is greater in those with large thrombi [*4*]. This is, of course, not always true of the individual case, and the diagnosis is rendered even more difficult by the fact that complications superimposed on mitral stenosis (coronary artery disease, embolization, pulmonary infection) may stimulate the symptoms of the ball thrombus.

In the patient presented today, the rapidly progressive cardiac failure suggests that the thrombus contributed to a further decrease of cardiac output over that caused by pure mitral stenosis of this degree. The shift of the nature of apical murmurs between the second and the third admission was probably produced by a change in size or position of the thrombus in relation to the mitral valve, and seems the best clinical clue to the diagnosis. Perhaps the firm attachment of the thrombus to the atrial wall prevented its extensive impingement upon the mitral valve and therefore precluded such dramatic clinical findings as postural syncopic attacks, symmetrical peripheral ischemia and cyanosis which have been occasionally described in such cases. Angina, considered a most prominent and helpful diagnostic sign in these patients, [*4*] was not noted. Other clinical findings were those related to advanced cardiac failure. Peripheral edema, serous effusions and marked congestion of lungs, liver and spleen were found at postmortem.

Large atrial thrombi are found at autopsy in 3 per cent of patients with rheumatic heart disease [*5*]. The cause of their formation is not known. Neither active rheumatic foci nor infarction are found in the underlying atrial wall. Wallach has advanced the theory that a jet lesion from a partially regurgitant mitral valve injures the endocardium, resulting in a sterile collagen degeneration of the endocardium (nonbacterial thrombic endocarditis, verrucous endocardiosis) which is then prone to formation of a thrombus [*5*]. No definite endocardial change of etiologic significance has been demonstrated at autopsy in these cases, perhaps because secondary anoxic changes in the endocardium which occur beneath any atrial thrombus tend to obscure such a change.

[1] O'Neal, R. M., Thomas, W. A., Lee, K. T. and Rabin, E. R. Alveolar walls in mitral stenosis. *Circulation*, 15: 64–67, 1957.

[2] Graef, I., Berger, A. R., Bunim, J. J. and De La Chapelle, C. E. Auricular thrombosis in rheumatic heart disease. *Arch. Path.*, 24: 344–365, 1937.

[3] Wallach, J. B., Lukarsh, L. and Angrist, A. A. Occlusive auricular thrombi. *Am. J. Med.*, 15: 77–82, 1953.

[4] Evans, W. and Benson, R. Mass thrombus of the left auricle. *Brit. Heart J.*, 10: 39–47, 1948.

[5] Wallach, J. B., Lukarsh, L. and Angrist, A. A. Formation of auricular mural thrombi. *Am. J. Med.*, 16: 543–548, 1954.

Case Reports

Skin-covered Mediastinal Teratoma Simulating a Fetal Parasite*

A Review of Mediastinal Teratogenesis

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In a recent review of the subject of mediastinal tumors we have made reference to a personal series of fifty-one such neoplasms [*1*]. Perhaps the most remarkable of these was a complex skin-covered teratoma that presented several features of unusual interest, the most notable being its gross resemblance to a so-called fetal parasite. Interestingly enough, the patient's complaints apparently arose not from the size and location of the tumor but from a severe lipoid pneumonitis that the tumor had produced in the adjacent lung. Being only the third skin-enveloped teratoma recorded in the literature it seems sufficiently unique to be deserving of a detailed report.

CASE REPORT

J. V. D., a thirty-one year old white male dental technician, was admitted to the hospital on April 24, 1952, with a chief complaint of right anterior chest pain accompanied by cough, fever and nightsweats, all of ten days' duration. The pain was pleuritic in nature; the cough productive of yellowish mucoid sputum. On the day of admission the patient had had a shaking chill. He consulted a private physician who obtained a chest x-ray and referred him to the hospital with a diagnosis of pneumonia, right middle lobe. Past history disclosed that he had experienced a similar but less severe illness four months earlier, at which time his symptoms had subsided spontaneously after five days' rest in bed.

On physical examination the patient was found to be acutely ill. The temperature was 103.8°F., pulse 120, respiration 24, blood pressure 130/75. Significant findings were limited to the right chest where there was a distinct lag in respiratory excursion, dullness to percussion and diminished tactile fremitus. Breath sounds were likewise suppressed on the right, to a greater extent anteriorly. A few coarse rales were audible along the right sternal border. No friction rub could be heard.

The white blood count was 10,800 per cu. mm. with 89 per cent neutrophils, but other laboratory studies were within normal limits. Sputum examinations were negative for acid-fast bacilli. Chest roentgenograms (Fig. 1) showed a large spherical density measuring 9 cm. in diameter in the anterior mediastinum plus another opacity in the region of the right middle lobe. Radiographic evidence of a rapidly accumulating effusion subsequently appeared (Fig. 2), but attempted thoracenteses at multiple sites obtained only 60 cc. of straw-colored fluid which proved to be sterile. With penicillin and streptomycin therapy the patient's fever and chest pain gradually subsided, but x-rays revealed a persistence of the mass in the right middle lobe.

On the fourteenth hospital day a right thoracotomy was performed, the right chest being entered through the bed of the subperiosteally excised fifth rib. The pleural space was obliterated by a thick gelatinous substance which was rather easily stripped off the underlying lung. A frankly purulent loculus was encountered in the oblique fissure and approximately 150 cc. of thick creamy pus was evacuated. A solid mass could be palpated within the middle lobe. In dissecting out the hilus for evidence of nodal involvement a tumor mass was found adherent to the

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FIG. 1. Posteroanterior and lateral chest roentgenograms showing a 9 cm. spherical density in the anterior mediastinum at the base of the heart. There is also a homogeneous opacity in the region of the middle lobe. The lower ovoid shadow seen in the lateral projection represents interlobar fluid.

pericardium. Further dissection revealed the remarkable appearance of the tumor with its skin-covered external surface. By a combination of sharp and blunt dissection the tumor was freed down to a thick fibrous pedicle extending posteriorly through the arch of the aorta. After securing the pedicle with suture ligatures it was divided and the tumor peeled out of its mediastinal and middle lobar bed with relative ease. Because of obvious necrosis in the middle lobe a lobectomy was performed. A decortication of the remaining lobes was completed and the chest closed in standard fashion. Recovery was uneventful. Four years postoperatively the patient remains clinically well and subsequent roentgenograms show no evidence of recurrent pleural or parenchymal disease. (Fig. 3.)

Grossly, the specimen consisted of a soft globular mass covered in greater part by skin presenting a few long hairs and many fine downy hairs. (Fig. 4.) In addition there were several bud-like projections and a small sinus. One portion of the tumor was devoid of apparent skin and in this area several well formed teeth were visible in association with a piece of bone. Near the teeth was an irregular red-colored protuberance which to the imaginative eye looked like a tongue. The cut surface of the tumor appeared largely lipomatous (Fig. 5) without any gross organoid structures. The middle lobe (Fig. 6) presented a central excavation with a necrotic lining.

Microscopically, the tumor was found to contain a variety of tissues. (Fig. 7.) Practically all portions of the tumor were covered with squamous epithelium. Bone and cartilage were seen as well as a number of embryonic teeth. Bronchial and gastrointestinal mucosa were readily demonstrable. Other tissues discernible were pancreas, salivary gland, skeletal muscle, cerebrum, cerebellum, a rudimentary eye and kidney. There was no evidence of malignancy. The resected middle lobe showed a severe lipoid pneumonia, apparently resulting from the sebaceous material secreted by the skin-covered surface of the tumor.

COMMENTS

In view of the frequency with which teratomatous elements can be demonstrated in the walls of dermoid cysts no rigid distinction should be made between dermoid cysts and teratomas, the entire group being more properly termed teratoid tumors or cystic and solid teratomas. Because of their extraordinary morphology these tumors have been reported with greater frequency than any other primary mediastinal neoplasm, so much so that one fairly recent communication on the subject concluded that they constituted virtually one-half of all mediastinal tumors [*2*]. However, to judge their

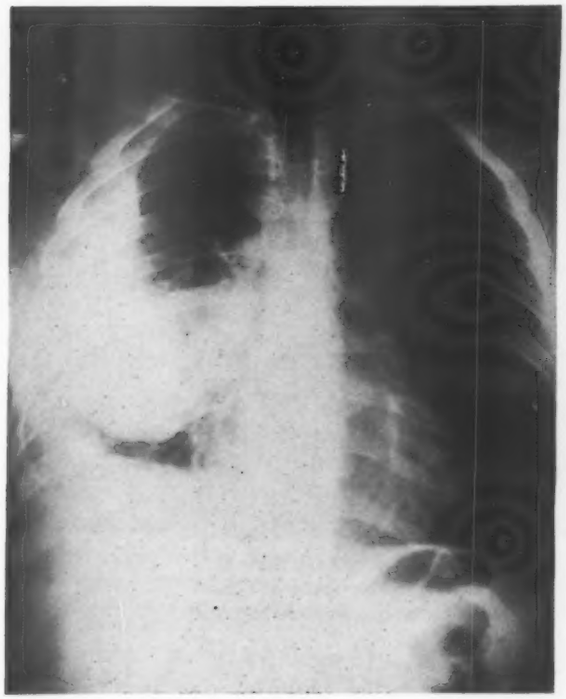

FIG. 2. Chest x-ray obtained one day later than Figure 1 showing the rapidly developing pleural effusion.

FIG. 3. Chest x-ray taken three years postoperatively. The patient remains well.

true incidence from the total number of cases reported is misleading, and a fairer estimate based on an analysis of collected unselected cases [*1*] shows teratomas to comprise 20 per cent of all primary mediastinal tumors, ranking second to neurogenic tumors in over-all frequency but first insofar as the anterior mediastinum is concerned.

More commonly cystic than solid, these tumors contain one or more cystic spaces filled with a grumous fluid containing sebaceous material, fat droplets, flakes of keratin and hair. The inner surface with its squamous epithelial lining may grossly resemble skin or present an orange peel appearance. In some instances the wall is lined not by squamous epithelium but by respiratory or alimentary tract mucosa or by nervous tissue, in which event it may then contain mucus or clear fluid resembling spinal fluid. Nodules of teratomatous tissue, including such startling organoid structures as well developed teeth and bone, may project inward from the wall. For clarity's sake it is quite important not to confuse other cystic mediastinal tumors with cystic teratomas. In reviewing the literature we have encountered not infrequent instances in which cysts made up entirely of bronchial or gastrointestinal elements have been misinterpreted as dermoid cysts instead of the bronchogenic cysts or enterogenous cysts that they actually represent. There is the same hazard in the case of mediastinal granulomas, for the caseous contents of such lesions can easily be mistaken for the grumous type fluid one associates with cystic teratomas. We believe, for instance, one of Heuer's classic cases represents just such a granuloma [*3*].

The solid teratomas tend toward greater complexity and may contain representative components of any organ thrown together in chaotic disarray. Even so, it is exceedingly rare for one of these tumors to present an external skin covering similar to the one described in this report. As far as we can determine only two comparable tumors have been previously reported. Von Török in 1900 reported the excision of a skin-covered "foetus in foetu" from the mediastinum of a four year old girl who unfortunately did not survive [*4*]. Because of the conformation of the tumor mass, part of which bore a vague resemblance to a human head while in other areas there were loops of intestine, the author believed that the tumor represented a parasitic included fetus. In 1933 Harrington [*5*] reported the successful removal of an anterior mediastinal teratoma from a seventeen year old girl. The

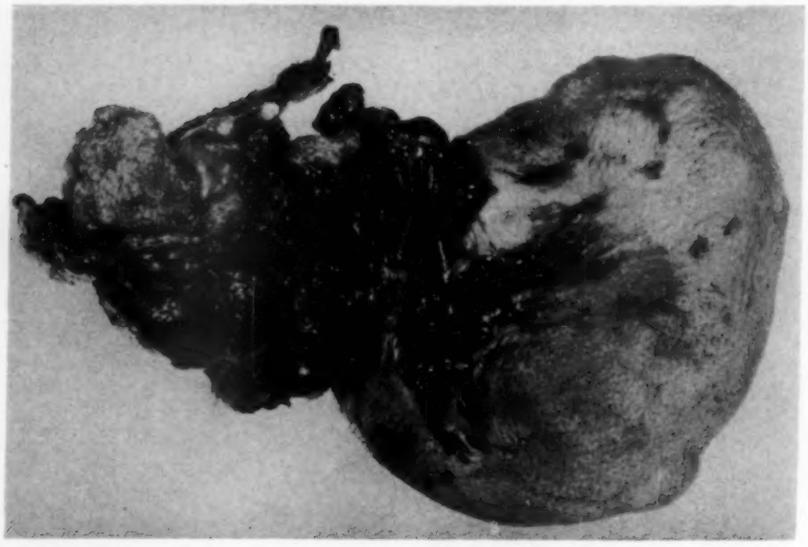

FIG. 4. Picture of the gross specimen illustrating the skin covering over the major portion of the tumor. A tongue-like protuberance is seen in the upper left hand corner just to the right of which are several teeth attached to a segment of bone resembling mandible.

tumor presented four bud-like outgrowths which the author interpreted as limbs, as well as sufficient organoid structure to suggest a "fetal parasite."

As one might anticipate from their remarkable appearance, the derivation of teratomas in general and especially those suggesting fetiformity has long provided a fertile field for speculation. The many aspects of this subject have been superbly summarized by Schlumberger [*6*]. The early concept postulated two distinctly different modes of origin for these tumors. Ovarian and testicular teratomas were considered to be of germ cell origin, while all other teratomas were thought to represent an included twin, the so-called fetal parasite or fetus in fetu. This latter view was originally proposed by Ekehorn [*7*] who had encountered several cases of such complex structure that he could not explain them on the basis of disturbed embryogenesis, hence the concept of an included twin. Many recognized authorities subsequently supported this view.

Later students of teratology, notably Nicholson [*8*] and Willis [*9*], challenged this hypothesis after meticulously analyzing many specimens without demonstrating conclusive evidence of true fetiformity. Nicholson [*8*] deprecated the general lack of objectivity in most descriptions of teratomas. "The proof of the presence of an organ in a teratoma is often enough contained in the bare statement that a structure resembles its somatic prototype. This is accepted by the writer and by others, as proof of identity, and he proceeds, generally in the same paragraph, to speak of it as the organ in question. . . . I am, indeed, prepared to assert that the greater part of the vaunted correspondence of these 'wonder tumors' with the head or hinder end of an embryo, as the case may be, rests on these insecure foundations." In his characteristically colorful style Nicholson stated further: "We are, if unconsciously, committed to certain theories of teratogenesis from the start, and find it difficult not to look for and find, strange and impossible likenesses to the human form. And since it is an amiable weakness of teratology to fancy that the words similarity and identity are synonymous, we readily see in a horrid tumour a smiling babe."

Willis [*9*] came to the same conclusion and cited the following reasons: (1) With extremely rare and doubtful exceptions teratomas exhibit no signs whatever of axiation, metameric segmentation or delamination, that is, the earliest and most fundamental features of the formation of a soma are lacking. (2) Teratomas possess no organs or true somatic regions. They contain masses of central nervous tissue but no brain, masses of bone but no bones, respiratory or intestinal cysts or canals but no proper trachea or intestinal tract, renal tissue but no

FIG. 5. The cut surface of the tumor discloses a complete lack of gross organoid structure.

FIG. 6. On cross section the resected middle lobe presents a central excavation in which the tumor was encased. Microscopically, the involved area of lung presented a severe lipoid pneumonitis presumably arising from the sebaceous material secreted by the tumor's skin covering.

kidney. (3) The multiplicity of certain constituents in teratomas is significant. If we postulate that a teratoma represents a malformed fetus, we must postulate further either that this fetus possesses an indefinite number of supernumerary organs or that the organs in question have suffered some kind of explosive disruption and scattering. (4) The anomalous absence of a particular tissue in certain teratomas is noteworthy. The "fetus" has successfully elaborated nearly all of its major "viscera" but not its skin, embryologically a strange omission indeed. (5) Abnormal tissue relationships and mixtures are frequent in teratomas, that is, a cavity may be lined by two or more totally distinct kinds of epithelium or there may be an admixture in one tumor of tissues of widely different degrees of maturity. These observations do not accord well with the fetal hypothesis, for we would have to assume not only that different tissues of the fetus ripen at different times and rates but that the unequal aging also effects contiguous areas of individual tissues. (6) Finally, it may be noted that incomplete examination of a teratoma may give it a false resemblance to a fetus. This last, like all the other points of distinction, is well exemplified by the specimen herein reported.

Years later Willis [*10*] added still other arguments against the fetal hypothesis: (7) The common sites of teratomas are not the sites of parasitic twins. (8) Most teratomas are known to arise during early stages of development when their bearers have no mature germ cells capable of parthenogenesis. (9) The view that they represent embryos completely ignores the important fact that they are true neoplasms, with powers of independent progressive growth which have never been observed in either "amorphi" or parasitic twins. There is then good evidence against, as well as a dearth of proof supporting, a relationship between teratomas and a so-called fetal parasite.

The foregoing applies to all types of teratomas, including mediastinal. Probably the most plausible theory of the genesis of those in the mediastinum is that championed by Schlumberger [*6*] who considers that all extragonadal teratomas result from local dislocation of tissues during embryogenesis, the proposed site of this maldevelopment in the case of the mediastinal teratomas being the branchial clefts. For several reasons the thymic anlage has been specifically incriminated: the thymus is one of the few organs comprised of cells from all three germ layers; the thymus is the only branchiogenic structure to descend routinely into the mediastinum; if carefully looked for, thymic tissue can almost always be found [*11*]; and in several instances well documented teratomas have been found imbedded in the thymus gland itself [*12–14*]. As additional proof of his contention Schlumberger [*6*] cites the frequent finding of pancreatic tissue within mediastinal teratoid tumors, a feature indicative of a strong entodermal influence such as that exerted over the thymus by the third

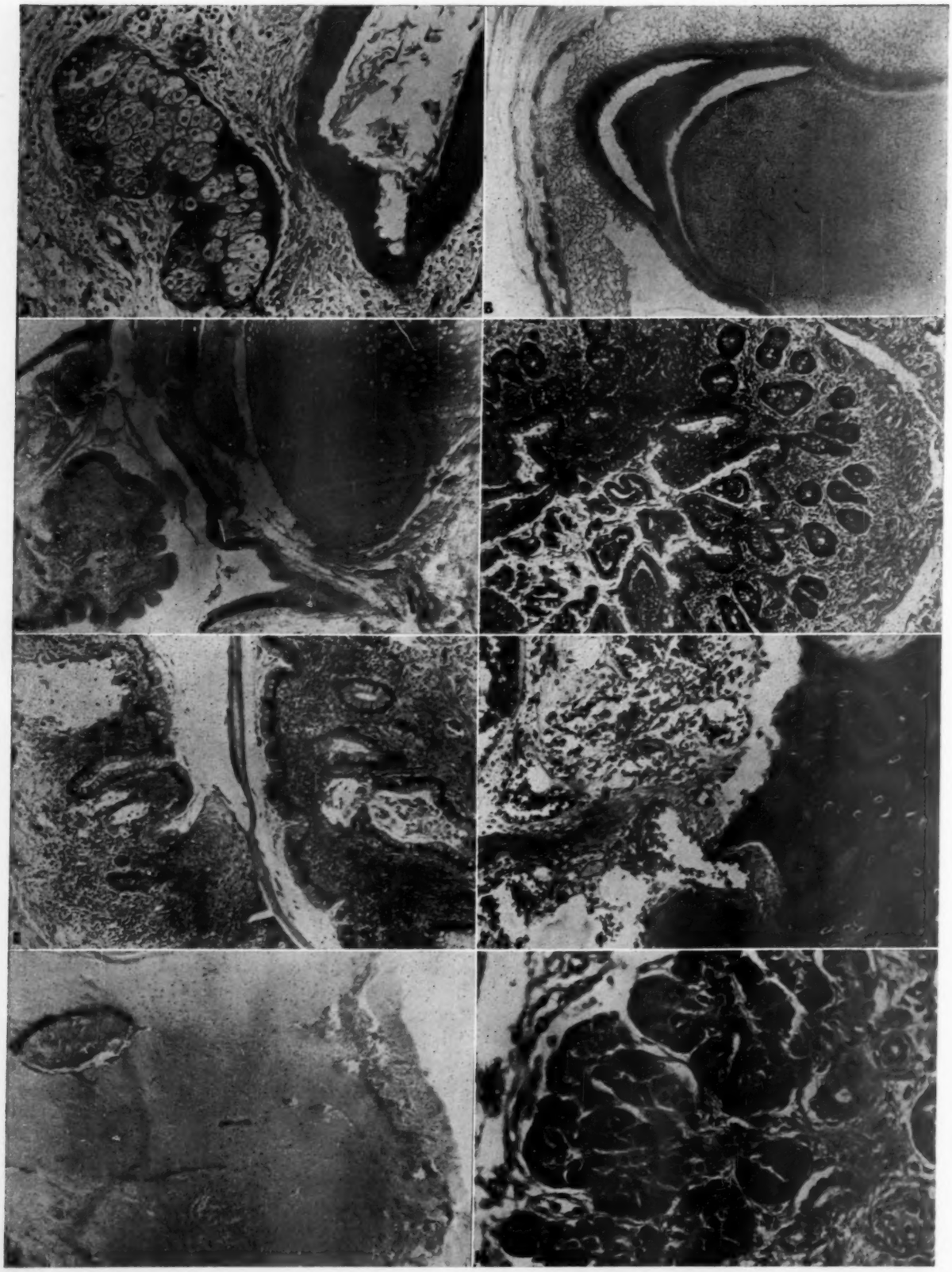

FIG. 7. Photomicrographs illustrating the wide diversity of tissues found within the tumor. A, skin. B, tooth bud, C, bronchial mucosa and cartilage. D, large intestinal mucosa. E, junction of squamous and columnar epithelium. F, bone marrow. G, central nervous tissue. H, pancreas.

pharyngeal pouch. It is even suggested that teratomas of this region might be more precisely identified as teratomas of the thymus. While agreeing with the site of origin, Friedman feels that the recently substantiated occurrence of primary mediastinal seminoma (germinoma) now enables one to ascribe a true germinal origin to thymic teratoid growths [*14*].

Whatever their precise derivation, intrathoracic teratomas are found almost exclusively in the anterior mediastinum where they may lie anywhere between the superior thoracic strait and the diaphragm, the most common site being in the middle third of the anterior mediastinum between the sternum and base of the heart. For one to reside in the posterior mediastinum is a rare finding [*16–22*]. Still rarer is their occurrence intrapericardially [*23–31*], although mediastinal teratomas in general almost uniformly present intimate adhesions to the pericardium and great vessels.

Symptoms are generally insidious in onset, seldom arise prior to puberty and, unless infection or malignant transformation intervenes, are not apt to be manifest until the third or fourth decades of life. In an elaborate review of the subject Rusby [*32*] computed a life expectancy for untreated mediastinal teratomas of 1.8 years after the onset of symptoms. Of a group of more than 200 such cases he could find only 3.3 per cent in which the tumor did not in some way contribute to the patient's death. Cough and anterior chest pain are the most common complaints. Dyspnea with or without true stridor may occur, sometimes only when lying supine. The expectoration of hair may provide startling as well as pathognomonic evidence of a cystic teratoma; this is more apt to arise in the neglected case judging from the 10 to 13 per cent incidence in the older literature [*32–34*] as compared with but 5 per cent in the more recent literature [*1*]. The color of the hair has no apparent relationship to the hair of the host; it is nondescript in most instances but occasionally blond and in one instance was red [*28*]. As a rule, rapidly progressive findings are indicative of malignancy, but on occasion benign teratomas may likewise cause violent symptoms, especially when infected. Rupture may occur into the mediastinum, lung, bronchus, pericardium, pleural space, chest wall and rarely even into the aorta or superior vena cava. The possibility of evacuation into the pleural space has recently been reemphasized [*35*]. We are aware of but one previously reported case in which a mediastinal teratoid tumor has given rise to a lipoid pneumonia [*36*]. Unlike that case, in which the lipoid material originated from intrabronchial perforation of a ruptured dermoid cyst, the lipoid granuloma accompanying the tumor reported herein resulted apparently from sebaceous material excreted by the encompassing skin, an etiology that seems unique.

Superior vena caval obstruction is common among malignant mediastinal teratomas but can result also from a benign teratoma. In much the same fashion benign teratomas have been associated with recurrent laryngeal nerve paralysis [*37*], phrenic nerve paralysis [*38*] or Horner's syndrome [*3*], emphasizing the importance of avoiding a premature declaration of malignancy, or worse yet, inoperability. Localized bulging of the chest wall is not uncommon [*32*] and may even antedate the onset of symptoms [*39*]. Also worth noting is the infrequent capacity of these tumors to present initially in the neck. This was true of the first mediastinal teratoma ever to be reported (Gordon, 1823) [*32*], in the case of a twenty-one year old girl in whom cough and tachycardia persisted following a bout of pneumonia. Later a small pulsatile tumor appeared in the suprasternal notch. Initially regarded as an aortic aneurysm, the mass gradually increased in size and ultimately ruptured with egress of serous fluid. At necropsy a cystic teratoma was found in the anterior mediastinum containing hair, sebaceous material, teeth and bone. In rare instances a mediastinal teratoma may attain sufficient size to be present primarily in the abdomen, as in one of Brantigan's cases [*40*].

Radiographically, the appearance of these tumors is usually that of a round or oval, sharply defined shadow projecting from either mediastinal border and confined in the lateral projection to the anterior mediastinum. Less often the outline is bosselated and in the presence of malignancy it is apt to be irregular. Ordinarily they are of homogeneous density but teeth, bone or bits of calcium are sometimes discernible. Needless to say, planigrams may be extremely helpful in the latter regard. In some instances the wall of cystic teratomas may be totally calcified. It is always important to realize that most of these tumors, because of their close apposition to the heart and aorta, seem to pulsate at fluoroscopy. Unless teeth are visualized a specific roentgenographic diagnosis is seldom possible preoperatively. A diagnostic aid reported by Phemister [*41*] in 1936, but never corroborated since then, consists of maintaining the patient motionless for an adequate length of time prior to obtaining an x-ray in order to stratify the fatty

content of a dermoid cyst and thereby obtain a fluid level, even though no air is contained in the cyst.

The malignant potentiality of teratomas in general is well documented. Concerning mediastinal teratomas, the incidence of malignancy is said to be approximately 12 per cent [*32,34*], and 70 per cent of these are said to originate in solid tumors [*32*]. Among unselected cases we have shown that closer to 20 per cent are actually malignant [*1*]. In view of the virtually endless variety of tissues included in these tumors, it is not surprising that almost any type of malignant tumor can occur. Epidermoid carcinoma and adenocarcinoma are probably the most common types encountered but undifferentiated carcinoma, neurofibrosarcoma, liposarcoma, rhabdomyosarcoma, hemangioendothelioma, among others, have been described. Cases have been recorded in which an apparently benign teratoma has been excised only to recur later as a frankly malignant tumor. Moreover, it is now clear that tumors identical with testicular tumors can arise primarily in the mediastinum, the authenticity of their mediastinal origin being predicated upon an absence of any semblance of tumor or scar in multiple sections of the testicles. The importance of this latter point stems from the fact that a primary tumor within the testicle may be extremely small, may revert to a benign tumor while the metastasis thrives, or may spontaneously regress and be represented solely by a fibrous scar [*42,43*], again without altering the progress of the metastatic foci. Because of inadequate examination of the testicles a number of alleged primary mediastinal choriocarcinomas (chorionepitheliomas) cannot be accepted as authentic [*44,45*]. However, there have now appeared enough well documented cases of primary mediastinal choriocarcinoma [*46–56*] and seminoma [*14,57,58*] to establish their existence beyond any doubt. As mentioned earlier, Friedman [*14*] interprets the very existence of primary mediastinal seminoma (germinoma) as evidence that all mediastinal teratomas originate in primordial germ cells.

Unless accompanied by such diagnostic leads as a history of hair-spitting or radiographic evidence of teeth, an absolute preoperative diagnosis is seldom possible. Whether or not the diagnosis can be established preoperatively is purely an academic question, however, for any indeterminate mediastinal tumor, be it teratoma or not, demands surgical excision. If one obtains reassurance from an absence of symptoms, apparent stability and the presence of calcification in such a tumor, he is poorly acquainted with their sinister inclinations. Maier [*38*], for example, has described a circumscribed calcified anterior mediastinal tumor that had been observed for four years without any visible enlargement being detected. When it ultimately grew larger, the patient was referred for thoracotomy. By that time it was too late, however, and resection was precluded by mediastinal and hilar involvement. The invasive component of the tumor proved to be an extremely anaplastic undifferentiated carcinoma arising in and extending through the wall of a benign-looking cystic teratoma.

In contrast to this last example, the case contained in the present report provides a gratifying contrast for the patient remains well four years later. There seems to be little justification, therefore, for a policy of "watchful waiting" and regardless of the presence or absence of symptoms, prompt surgical excision would seem to constitute the most rational approach to any indeterminate mediastinal tumor.

SUMMARY

1. This report concerns a benign skin-covered mediastinal teratoma bearing a remarkable resemblance to the so-called "fetal parasite." As far as we know this is only the third such case ever to be reported in this location. An interesting sidelight was the lipoid pneumonia which the tumor produced in the middle lobe due apparently to the liberation of sebaceous material by the outer covering of skin. The patient remains well four years following excision of the tumor and the middle lobe.

2. The subject of mediastinal teratomas is reviewed, particular attention being devoted to their derivation.

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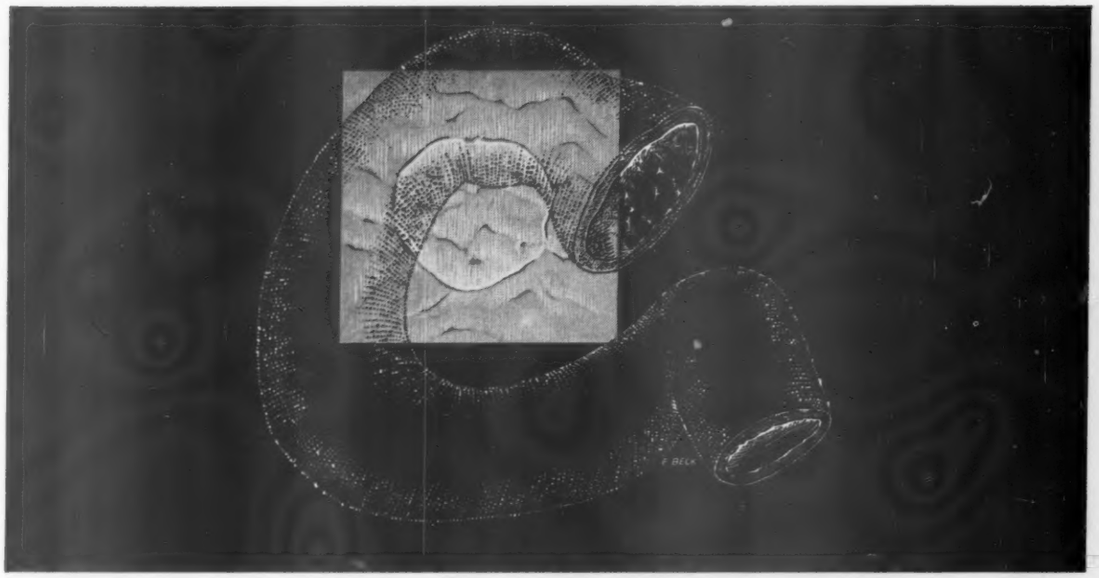

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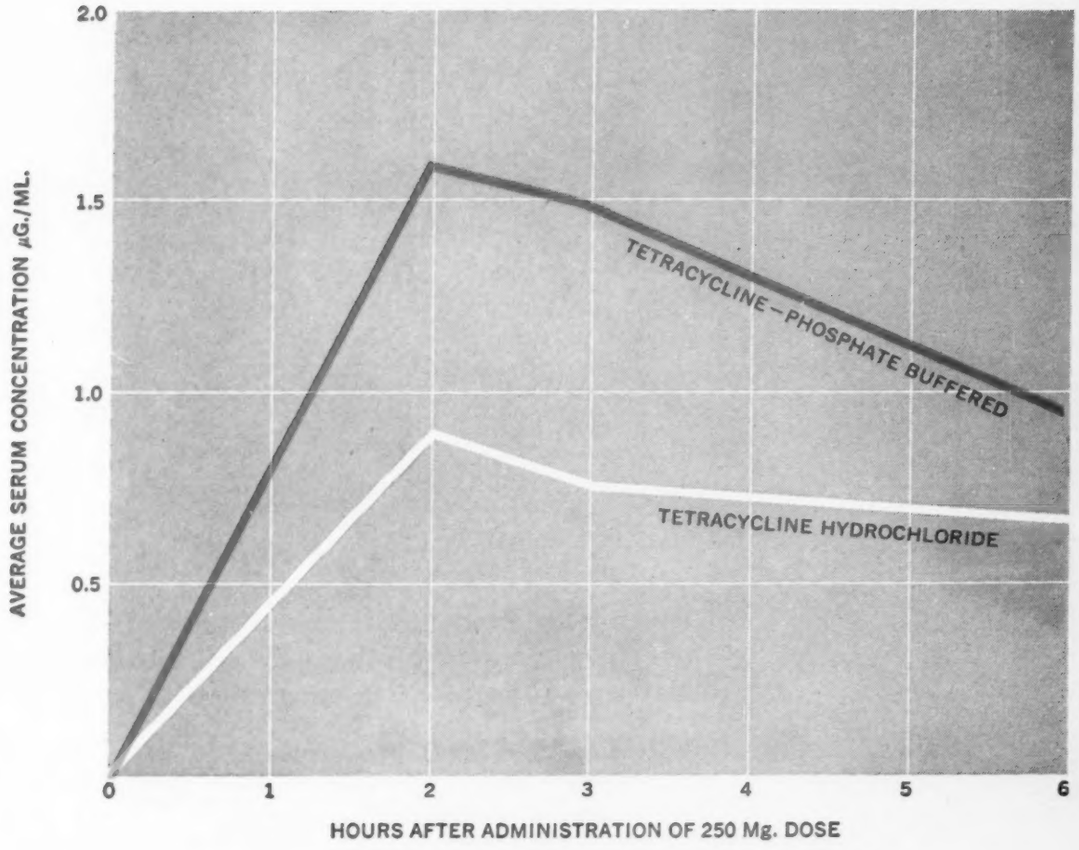

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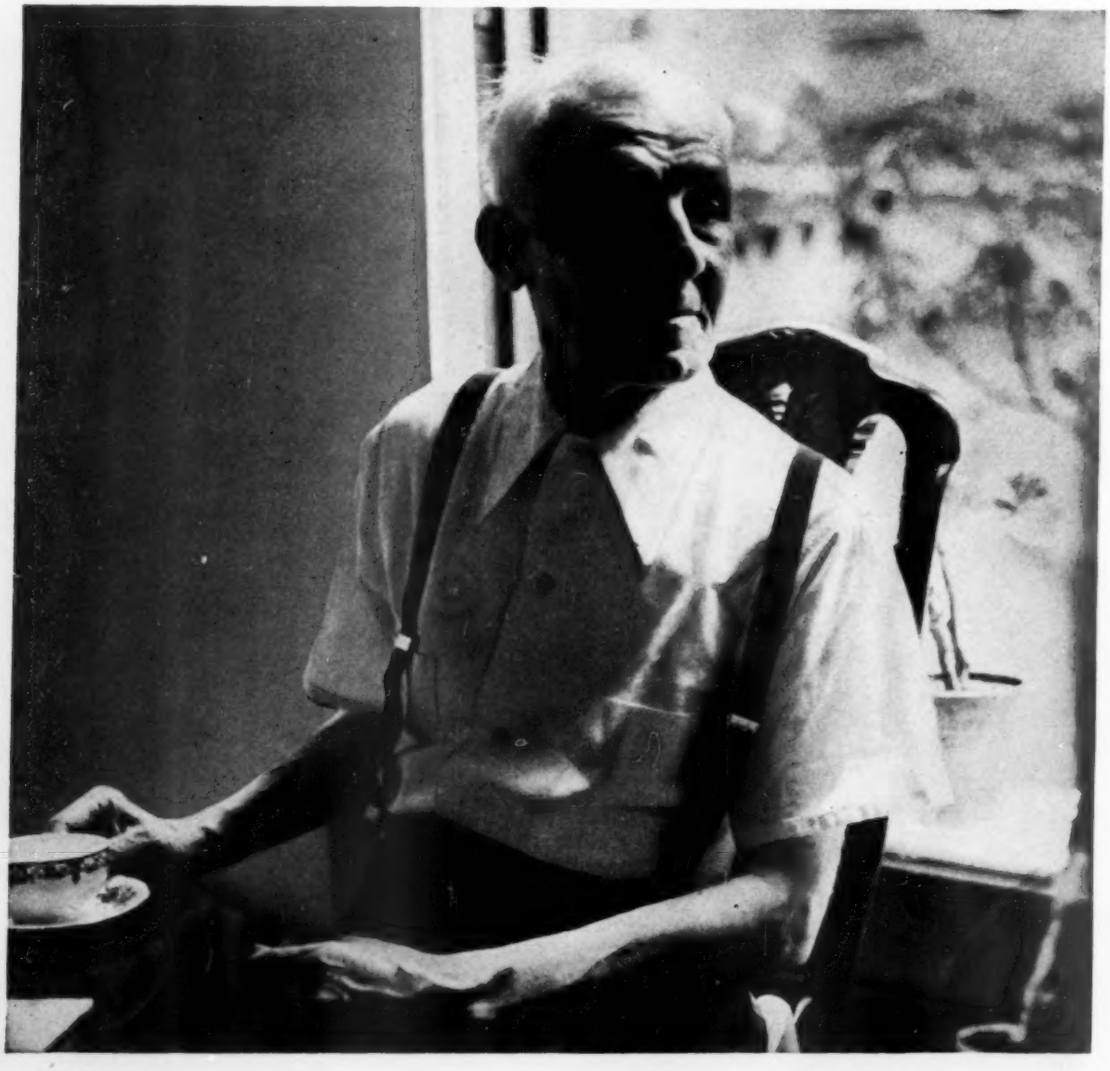

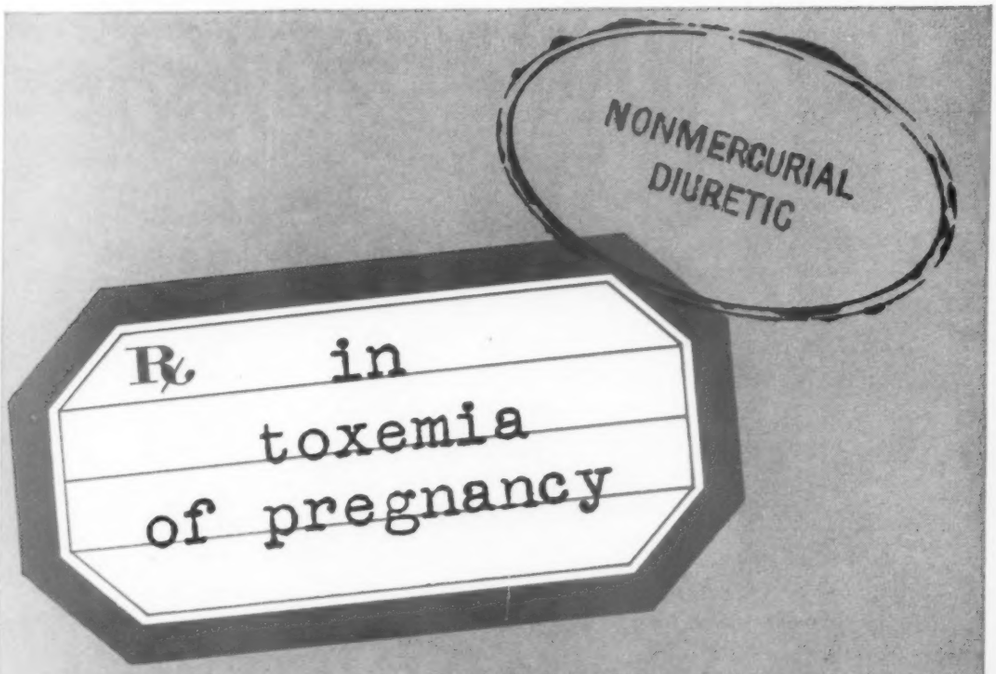

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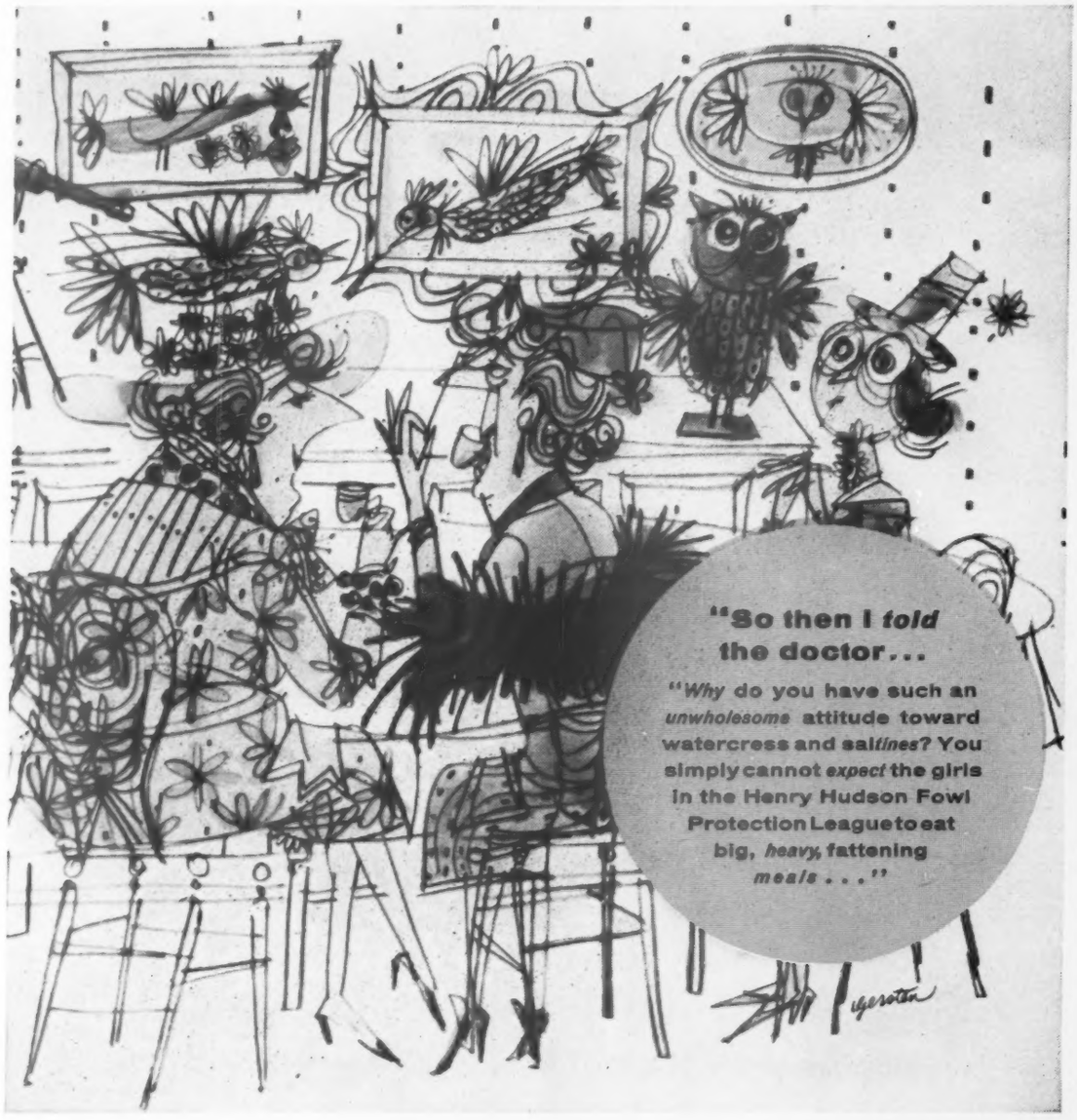
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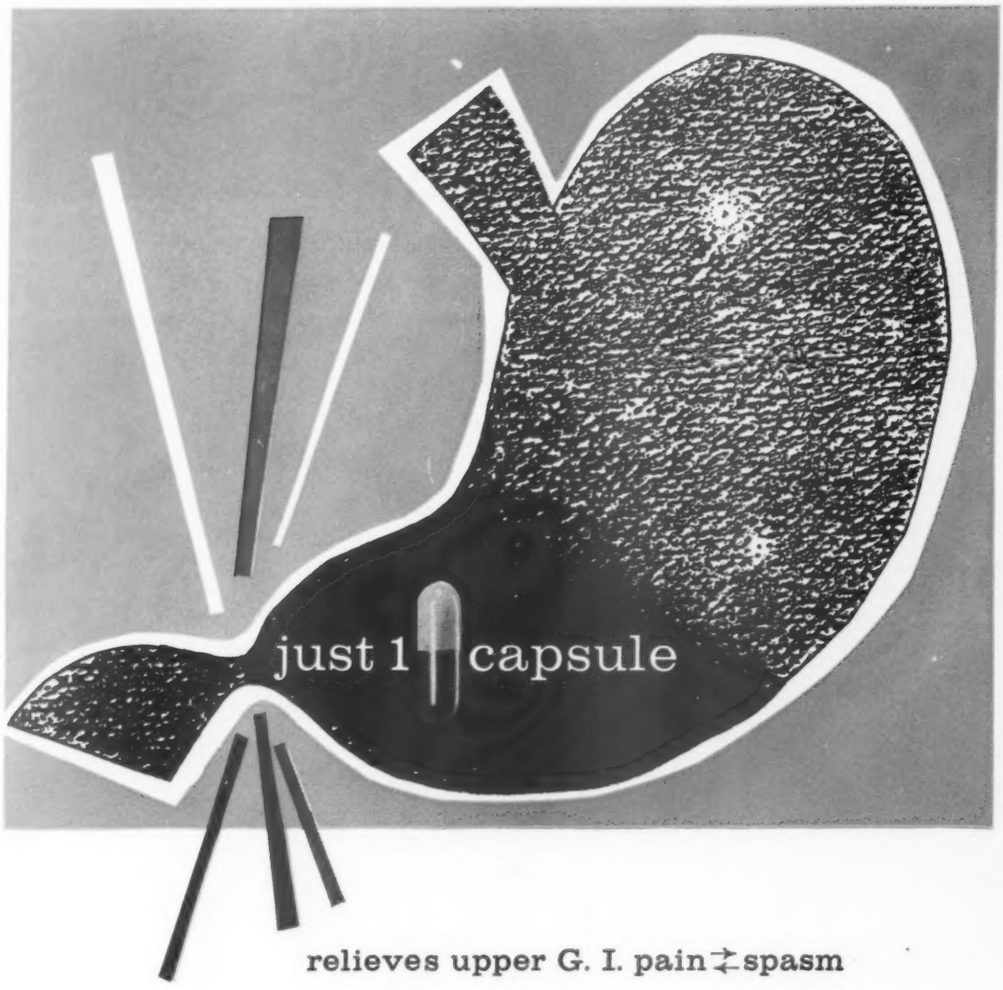

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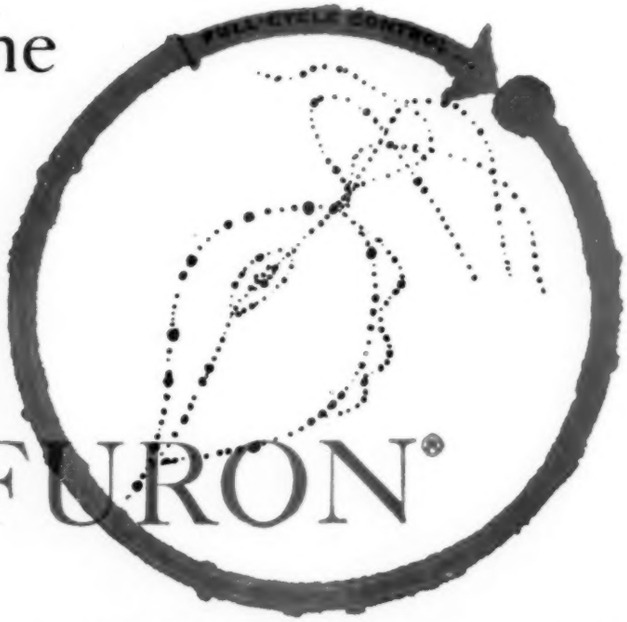

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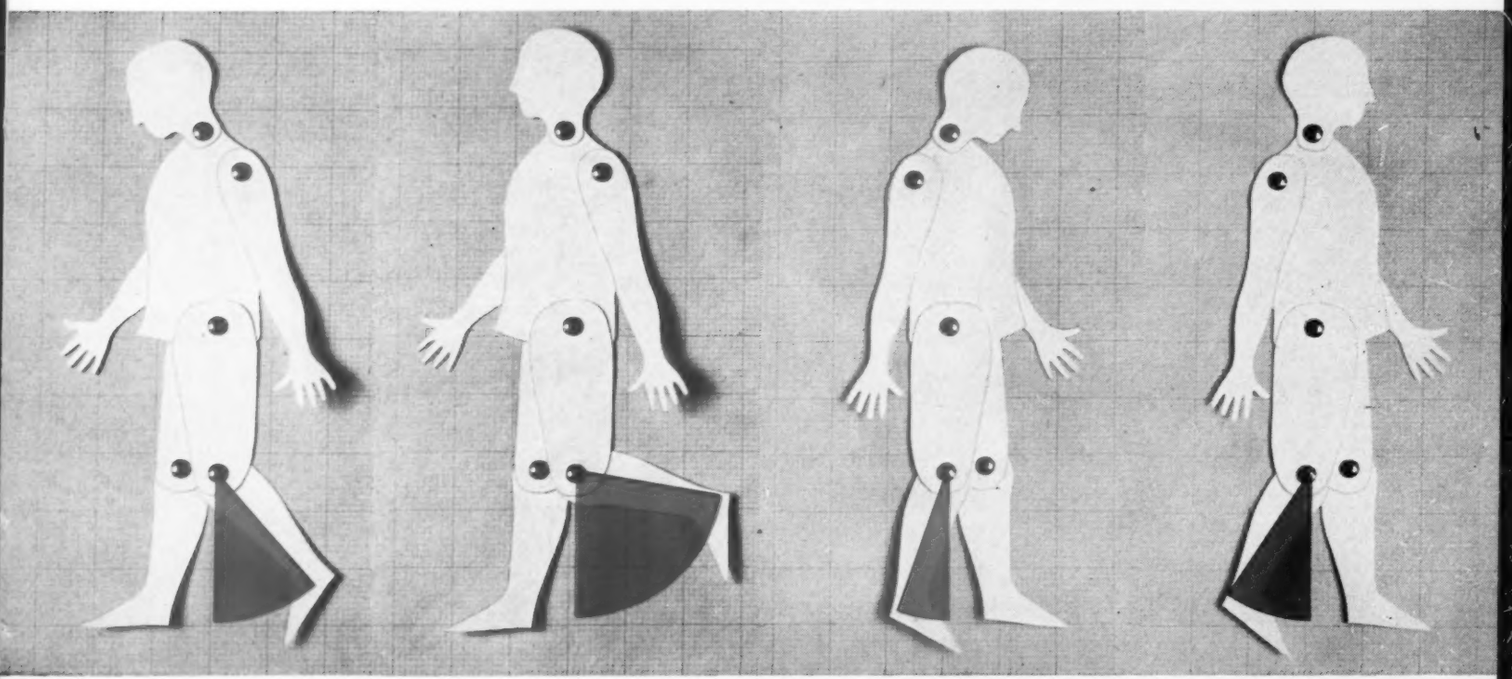

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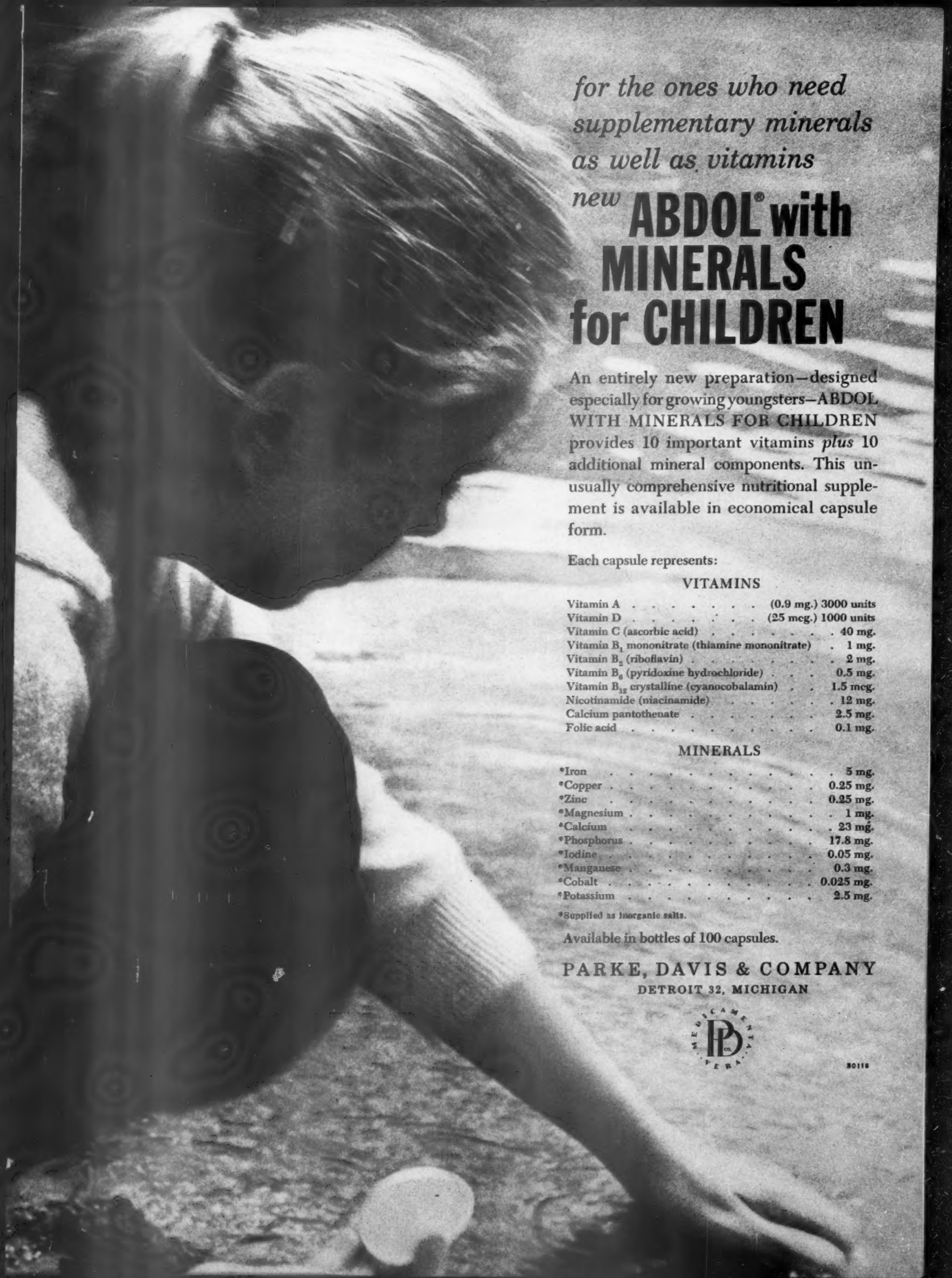

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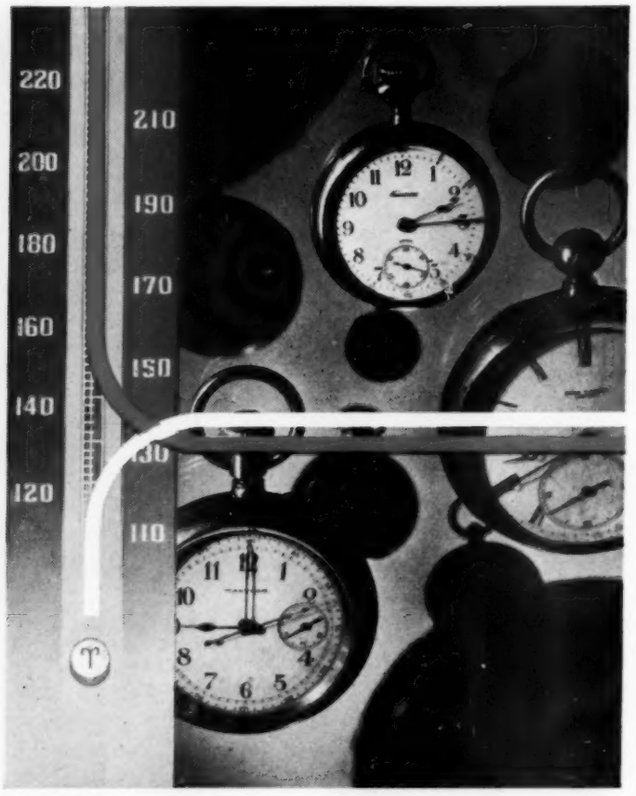

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1. Spiesman, M. G. and Malow, L.: Amer. J. Proctology, June 1956.

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References: (1) Russek, H. I.; Zohman, B. L.; Drumm, A. E.; Weingarten, W., and Dorset, V. J.: Circulation *12*:169, 1955. (2) Dripps, R. D.: J.A.M.A. *139*:148, 1949. (3) Deitz, G. W.: Am. Pract. & Digest Treat. *6*:1872, 1955. (4) Lewis, B. I.; Lubin, R. C.; January, L. E., and Wild, J. B.: Circulation *14*:227, 1956.

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For references and complete information concerning dosage, indications, side effects, and contraindications, write V. D. Mattia, Jr., M.D., Director of Medical Information, Hoffmann-La Roche Inc, Nutley 10, New Jersey.

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Professional literature is available upon request. Harmonyl is supplied in 0.1-mg., 0.25-mg., and 1-mg. tablets. Abbott

References: 1. Communication to Abbott Laboratories, 1956. 2. Ferguson, J. T.: Comparison of Reserpine and Harmonyl in Psychiatric Patients: A Preliminary Report, Journal Lancet, 76:389, December, 1956. *Trademark

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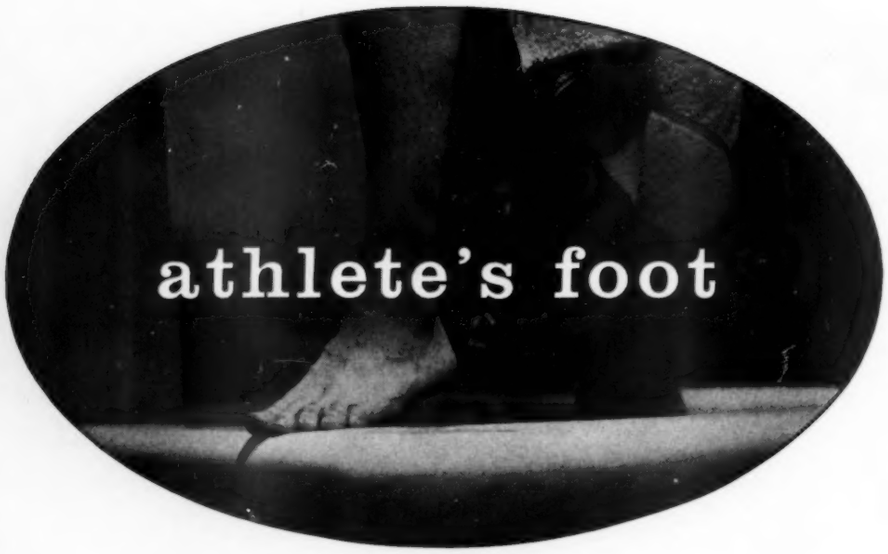

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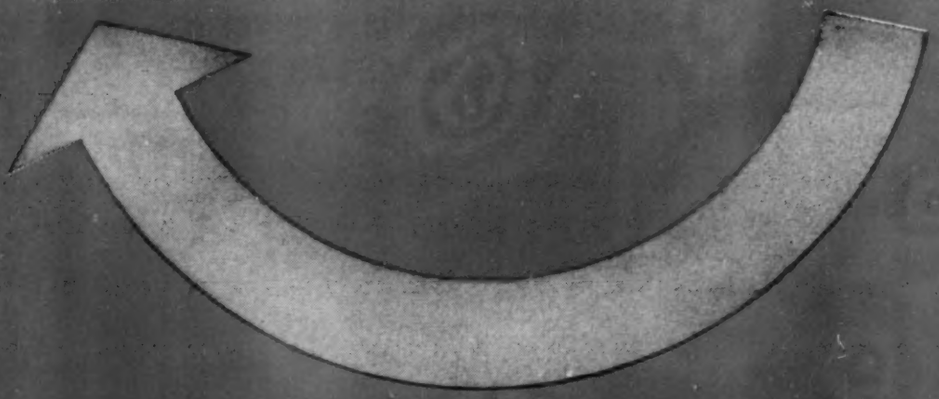

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Marquis, D. G., Kelly, E. L., Miller, J. G., Gerard, R. W. and Rapoport, A.: Ann. New York Acad. Sc. 67:701, May 9, 1957.

2 **"Since it [meprobamate–'Miltown'] does not cloud consciousness or lessen intellectual capacity, it can be used . . . even by those busily occupied in intellectual work."**

Keyes, B. L.: Pennsylvania M. J. 60:177, Feb. 1957.

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Sokoloff, O. J.: A.M.A. Arch. Dermat. & Syph. 74:393, Oct. 1956.

4 **"It ['Miltown'] . . . does not cloud the sensorium, and has a helpful somnifacient effect devoid of 'hangover'."**

Kessler, L. N. and Barnard, R. D.: M. Times 84:431, April 1956.

5 **"In anxiety and tension states, meprobamate relaxes without dulling cortical function to the same extent as the commonly-used barbiturates."**

Rindskopf, W., Ravreby, M., Gutenkauf, C. and Sands, S. L.: J. Iowa M. Soc. 47:57, Feb. 1957.

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1. Moyer, J.H.: J. Louisiana M. Soc. *108*:231 (July) 1956.

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2. Wright, W.T., Jr., et al.: J. Kansas M. Soc. *57*:410 (July) 1956.

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